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THE  
**LARYNGOSCOPE.**

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**STUDIES CONCERNING THE ACTION OF THE  
MUSCULUS CRICOHYREOIDEUS.\***

KURT TSCHIASSNY, M.D.,  
Cincinnati.

These studies originated from an epistolary controversy between the writer and Dr. Joel J. Pressman. This controversy was initiated by Pressman's<sup>1</sup> article on the "Physiology of the Vocal Cords in Phonation and Respiration." A short abstract of this exchange of letters, as far as is necessary for an understanding of the underlying subject, will be given. These differences of opinion were also the occasion of several experiments performed in collaboration with the late Dr. Samuel Iglauer and with Dr. Dennis E. Jackson. The results of these experiments were cinematographed, and the film has been shown on various occasions. A discussion of these experiments will be given.

I.

*History:* Our knowledge of the cricothyroid muscle goes back to the days of Andreas Vesalius,<sup>2</sup> "the father of anatomy" in the first half of the sixteenth century. In his famous book, "De Corporis Humani Fabrica," he describes this muscular structure as consisting of two pairs of muscles. Jacob Henle<sup>3</sup> in his classic, "Handbuch der Eingeweidelehre, 1873," introduced the terms "cricothyreoideus rectus" and "cricothyreoideus obliquus." He regarded this muscular mass as consisting of two separate parts united by connective tissue

\*From the Departments of Otolaryngology and Pharmacology, University of Cincinnati, College of Medicine.

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and vessels. Luschka<sup>4</sup> also held to the differentiation of the "musculus cricothyreoideus anticus rectus" and "musculus cricothyreoideus anticus obliquus." He called it "anticus" in order to differentiate it from the cricothyreoideus posticus which later was called ceratocricoideus and which represents an occasionally observed portion of the posterior cricoaryteoid (posticus) muscle.

*Anatomy:* Later anatomists abandoned the notion that this muscular structure consisted of two separate muscles. They assumed that this muscle is usually divided into a superficial medial vertical portion and a deeper lateral oblique portion. The distinction may be very striking or may be wanting. According to B. A. N. it is now called "pars recta" and "pars obliqua" respectively. Even the so-called "pars recta" has a distinct oblique course. The muscle originates at the cricoid ring close to its midline and is inserted at the inferior border of the thyroid cartilage, about 8 mm. distant from the midline. Occasionally fibres of this muscle extend downward to the upper tracheal rings or even to the isthmus of the thyroid gland, in some cases crossing the midline. These anomalies are called by Luschka "musculus thyrotrachealis, levator glandulae thyroideae and musculus thyroideus transversus respectively." The oblique portion starts on the outer surface of the cricoid cartilage and is inserted at the lower border and partly on the inner surface of the thyroid cartilage extending from the processus marginalis as far as the tip of the inferior horn. This portion is usually connected by some tendinous fibres with the lower portion of the constrictor pharyngis inferior (musculus cricopharyngeus) to which it is of course genetically related. The French physiologist Longet<sup>5</sup> found that this muscle is the only one supplied by the superior laryngeal nerve; all the other intrinsic laryngeal muscles are supplied by the inferior laryngeal nerve. As will be shown later, this muscle should be called: "Musculus thyrocericoideus on account of its mode of action."

*Mode of Action:* The manner in which this muscle works aroused the interest of the anatomists, physiologists and laryngologists for centuries.

There is a remarkable disproportion between the size of this muscle and the volume of the literature dealing with it. The famous Danish anatomist Jacob Benignus Winslow<sup>6</sup> (1669-1760) made the remark: "Les cricothyroïdiens sont disposer d'une facon qu'il est difficile de determiner leur usage."

While it was generally assumed that this muscle by its contraction approximates the thyroid cartilage and the cricoid ring to each other, there was a diversity of opinion concerning which is the fixed and which the moving structure.

Three different opinions were maintained in the literature: The oldest view regarded the thyroid cartilage as the moving structure. Exponents of this idea are according to Jurasz:<sup>1.c.</sup> Verheyen, Santorini, Meckel, Henle, Hyrtl, Hollstein, Leube, Landois, Herrmann, Ludwig, Gritzner, Rossbach, Merkel, Türck, Stoerck, Schrötter, Semeleder, Mackenzie.

At the beginning of the nineteenth century the idea was introduced that the cricoid was the moving structure. This was maintained by Th. Bartolinus, Heister, Magendie, Arnold, Harless, Fournier, Longet, Gavarret, Schech, Jelenffy, Elsberg, Hooper, Zuckerkandl, Neumayer. There was also a group represented by Winslow, Albinus, Hildebrandt, Quain, Budge, Mandl, Funcke, Gottstein, who assumed both ways.

Magendie<sup>7</sup> (1813) was the first to observe in animals that the cricoid ring moved, while Malgaigne<sup>8</sup> (1831) was able to show that this movement occurred in the act of swallowing as well as in phonation. These observations were repeated and substantiated by the experiments of Longet,<sup>5</sup> Schech,<sup>9</sup> Schmidt,<sup>10</sup> Jelenffy,<sup>11</sup> Neumayer<sup>12</sup> and others. Hooper,<sup>13</sup> of Boston (1883), deserves credit for having been the first to show by exact kymographic records the movement of the cricoid ring when the cricothyroid muscle was electrically stimulated directly or indirectly. Since the point of origin is the thyroid cartilage, and the point of insertion the cricoid ring, this author correctly suggested that it be called the "thyrocricoid muscle."\*

*Dissenting Views:* It seems, therefore, hard to understand why, at the present time, a number of textbooks and promi-

\*The same view was held by A. Jurasz. As a matter of fact, he called his article "Zur Frage Nach der Wirkung der Mm. Thyreocricoides." (I.c.)

nent authors still hold to the concept of the thyroid cartilage as the moving structure. For instance, we read in E. B. Gleason, Saunders, 1907: "The action of this muscle is to tilt the thyroid forward upon the cricoid. . ." A. Coolidge, Saunders, 1915: "The cricothyroid brings together the margins of the thyroid and cricoid cartilage. The cords . . . are made tense as the thyroid cartilage is pulled forward." McKenzie, Mosby, 1928: "The normal contraction of the cricothyroid muscle draws down the thyroid cartilage over the cricoid." W. W. Morrison, Saunders, 1938: "The tension of the cords is largely increased by the contraction of the two cricothyroid muscles which pull the anterior part of the thyroid cartilage down and lengthen the distance."

Robert Curry in his monograph, "The Mechanism of the Human Voice," (1942) Green and Co., New York: "If the cricoid is held fixed by the infralaryngeal muscles the anterior notch of the thyroid is drawn down and the thyroid pivots and slides on the cricoid. If the thyroid is held by the supralaryngeal muscles the cricoid is drawn upward in the neck. . ." While the latter part of this statement is to be accepted, the former is hard to understand since there does not exist an infralaryngeal muscle which can hold fixed the cricoid cartilage. In this respect Hooper already had emphasized: "With the exception of a small part of the inferior constrictor, not a single extrinsic muscle is attached to the cricoid cartilage. It is difficult to comprehend by what mechanism it can possibly be fixed in a sense that would permit the thyroid to be pulled down upon it." Negus,<sup>14</sup> however, in his monumental book, explains: "The cricoid cartilage is held back with great force against the front of the vertebral column by contraction of the cricopharyngeus muscle. Consequently, it is the thyroid cartilage which moves as a result of contraction of the cricothyroid muscle except during deglutition."

In conformity with this, the textbook of St. Clair Thomson and Negus<sup>15</sup> teaches: "During phonation the cricopharyngeus muscle holds the cricoid in place, bracing it back firmly as if to attach it to the vertebral column. In this action the thyroid

cartilage pivots on the cricoid, but during deglutition the cricopharyngeus muscle relaxes and the cricoid then pivots on the thyroid. . . ."

Finally, attention is called to the article of Chevalier Jackson<sup>16</sup> on the "Myasthenia Laryngis." He regards the assumption that the cricothyroid muscle creates tension of the vocal cords as one of the numerous misconceptions of the laryngeal phonatory mechanism. Jackson himself thinks that its action is to resist the orbicularis effect of the thyroarytenoid, the lateral cricoarytenoid and the interarytenoid by pulling the thyroid cartilage forward as the posterior cricoarytenoid pulls backward.

## II.

*Pressman's Theory:* Although there existed and still exists diversity of opinion as to which one is the moving structure and which the fixed, there is consensus throughout the centuries on two principal points: 1. Contraction of the cricothyroid muscle effects approximation of the two cartilaginous structures toward each other. 2. Approximation of those structures (narrowing the cricothyroid gap) effects elongation of the vocal cords.

Surprisingly enough, Pressman's explanation of the action of this muscle in his article referred to above maintains just the opposite. He says: "The thyroid cartilage is capable of superoinferior rotation on its cricothyroid joints. When the posterior fibres of the cricothyroid muscles exert their downward pull on the alae and inferior cornua of the thyroid, this cartilage undergoes a rotary movement which tends to pull the posterior portion of the cartilage downward and forward as a result of which the anterior portion, to which the anterior extremities of the vocal cords are attached, rotates upward. This rotary upward movement of the anterior insertion of the vocal cords on the thyroid cartilage increases the distance between this point and the side of the posterior insertion of the cords on the arytenoids (Fig. 8). . . ."

Two diagrams illustrating this description are added. The legend of the diagrams reads as follows: ". . . the contracted

thyrocricoid muscle tilts the thyroid cartilage, widening the cricothyroid gap and rotating the anterior insertion of the vocal cords upward over the arc of a circle. . . ."

Accordingly, Pressman assumes: 1. Contraction of the cricothyroid muscle effects separation of the two cartilaginous structures from each other. 2. Separation of those structures ("widening of the cricothyroid gap") effects elongation of the vocal cords. He does not explain the action of the anterior portion. There is no mention of any observations or studies by which the author was led to assume his divergent view; in fact, he does not even emphasize that his concept is not consonant with the view held by all previous investigators.

*The Writer's Objections:* In my opinion Pressman's theory could not be accepted unless the following objections were cleared up:

1. The cricothyroid joint is a hinge joint permitting only superoinferior rotary movements. It is enclosed by a capsule which is strengthened by the ceratocricoid ligaments. The assumed movement of the inferior horn, as indicated in Pressman's diagrams, represents an anterior dislocation of this joint, possible only after a rupture of the capsule and its ligaments.
2. It was heretofore generally assumed that the muscle by its contraction approximates the cartilaginous structures, whereby, in the resting state, the gap is wider than during contraction. Moreover, these distances have been measured accurately by Jörgen Möller and Fischer:<sup>17</sup> In the resting state, 14 mm.; in normal mechanism at A . . 8 mm.; in normal mechanism at a . . 6.5 mm.
3. The action of the anterior portion is not mentioned in the article. Assuming, as Pressman does, that the thyroid cartilage is the moving structure, it would result in a downward pull of this cartilage, thus opposing the action of the posterior portion; but an action of the posterior portion of the muscle, antagonistic to the action of the anterior, cannot be understood for the reasons shown in the diagrams (see Figs. 1 and 2).

FIG. 1.

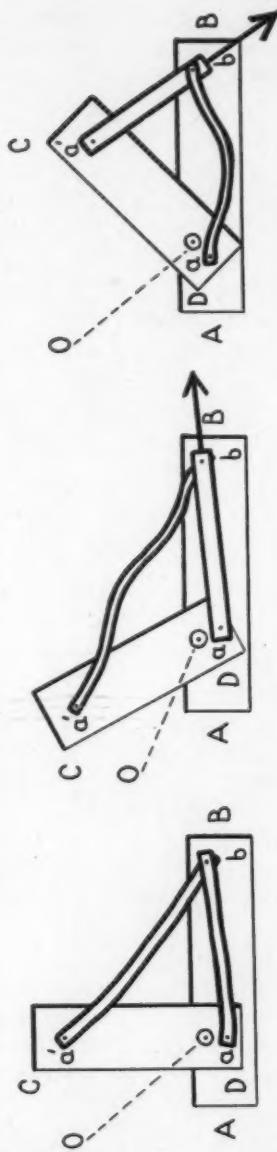


FIG. 2.

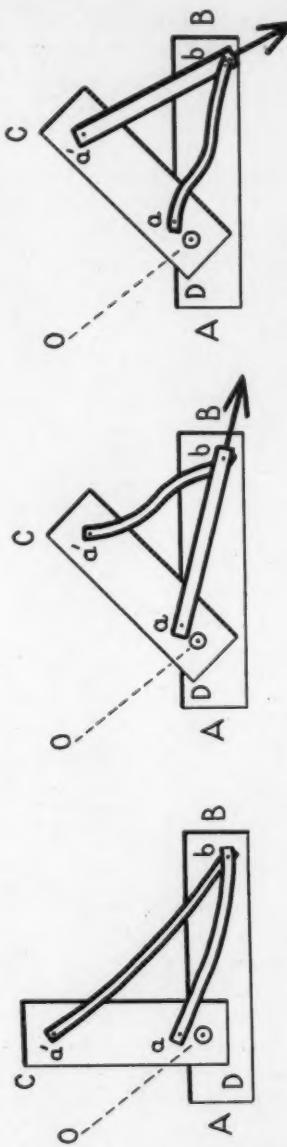


Fig. 1 represents a simplified reproduction of the mechanical system we are dealing with. AB and CD articulate about the axis O by means of the two ribbons ab and a'b. It makes no difference whether the ribbon ab or a'b produces the pull, the effect is a downward pull of the part CD around the

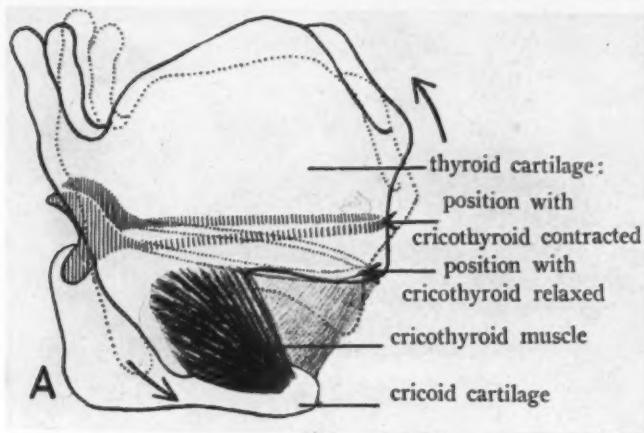


Fig. 3A. Reproduction of Pressman's diagram 8A.

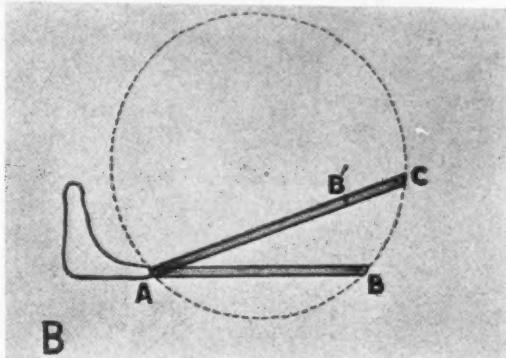


Fig. 3B. Reproduction of Pressman's diagram 8B.

point O toward the point b. Only if the arrangement were as indicated in Fig. 2 (*i.e.*, the insertion of the ribbon ab below the joint and the ribbon a'b above the joint) would there be

an antagonistic action of those two ribbons; however, an arrangement like that does not exist anatomically.

4. The thyroid cartilage is a rigid structure. The axis of rotation of this structure passes through the tips of the inferior horns; therefore, both the anterior and the posterior portion of the thyroid are moving in the same direction but cannot move in directions opposite to each other.

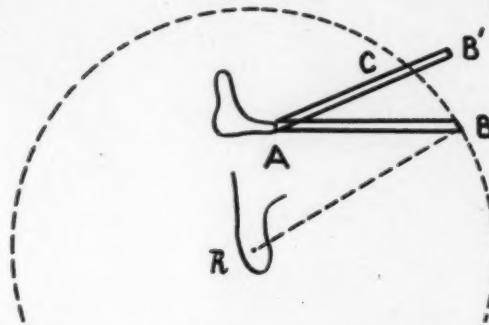


Fig. 4. (R) represents the point of rotation at the tip of the inferior horn. Upward movement around the axis of rotation (RB) brings the point (B) in the position of (C). The line (AB) is shorter than the line (AB') by the distance (CB').

5. In Pressman's diagrams 8A and 8B (reproduced as Figs. 3A and 3B) a rotation about an imaginary fixed point which does not exist is assumed. The only point of rotation is the cricothyroid joint located at the tip of the inferior horn; therefore, the diagram 8B should be constructed as shown in Fig. 4. Accordingly, the result of upward movement of the thyroid cartilage will be a shortening of the distance between vocal process and the point of anterior attachment, and consequently a relaxation of the vocal cords will take place.

I informed Dr. Pressman by letter of my objections and asked his explanation of the points not understood by me and some of my associates (*e.g.*, Dr. Iglauer and Dr. Ruth).

I sent Dr. Pressman a model constructed for this purpose, showing how, by approximation of the cartilaginous structures, lengthening of the vocal cords is effected. Fig. 5A and

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Fig. 5B is a photograph of this model. Although rather primitive, it is of value as an aid in explanation.

My letter to Dr. Pressman initiated a most interesting and stimulating epistolary discussion. Numerous letters were exchanged. It is beyond the scope of this article to present

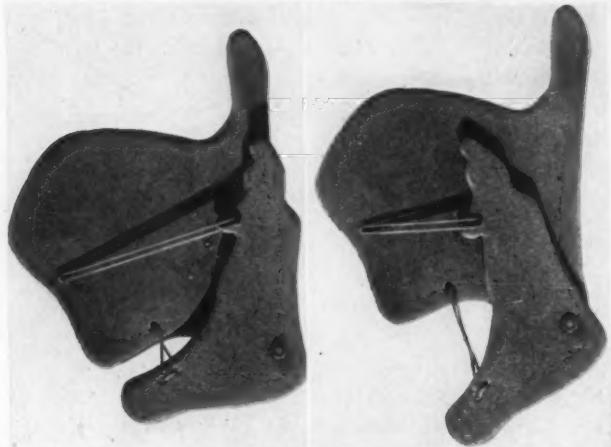


Fig. 5A. In this working model is shown how approximation of the cricothyroid ring toward the thyroid cartilage effects elongation of the vocal cords.  
Fig. 5B. Separation of the structures effects relaxation of the vocal cords.

a detailed account of their contents. Our correspondence came to a happy end when Dr. Pressman agreed that my main objections were justified. In his letter of March 30, 1943, he wrote: ". . . I appreciate your help and suggestions very much indeed and have given them frank expression in the chapter for Coates' Encyclopedia. For the most part, I have incorporated all the principles you have held to be true. You will dislike only the fact that I have retained the use of

Footnote: It seems to me of importance, especially for future investigators on this subject, to realize the fact that the principles as maintained by Dr. Pressman in his original article have been considerably modified by the author.

Moreover, I know very well that this report is in accordance with the tendencies of Dr. Pressman. When he acknowledged that my arguments were justified, he was fair enough to offer me some opportunities for publishing my objections; e.g., he wrote in his letter of June 18, 1942: ". . . when the next review is written I shall ask you to be kind enough to review my article, and will publish your criticisms under your name as you see fit to write them, with no changes whatsoever. At that time I will add that your criticisms are justified by the facts and that current opinion should be guided accordingly . . ."

Fig. 8B since almost everyone else liked it . . ." Dr. Pressman was correct in supposing that I would not like the use of Fig. 8B. I still feel that this diagram illustrates just those principles which admittedly he has abandoned. Would it not be advisable to use a diagram somewhat like Fig. 4?

### III.

*Experiments:* In one of my letters I suggested to Dr. Pressman that he approach the problem experimentally, by electrical stimulation of the cricothyroid muscle in dogs. As I have already mentioned, this experiment has been performed by numerous investigators. I wrote to Dr. Pressman as follows: "It would probably be an interesting task for you to record cinematographically this experiment. It is really impressive." When Dr. Iglauer generously provided the opportunity, we made these experiments in collaboration with Dr. Jackson in the pharmacological laboratory of our university. The cinematographs\* were taken by Mr. Joseph B. Homan. The pictures were shown on various occasions.

In addition to examining and photographing the action of the muscle when stimulated *in toto*, we gave special attention to the action of the pars recta and the pars obliquus separately. To this end we removed one or the other portion. Such experiments have not previously been reported.

#### RESULTS OF EXPERIMENTS.

The results of our experiments performed on 12 dogs and shown in moving pictures are as follows:

1. Stimulation of the cricothyroid muscles approximates the cricoid ring to the lower border of the thyroid, the former being the moving structure.
2. Unilateral stimulation of the cricothyroid muscle effects elevation and deviation of the ring toward the stimulated side.

\*This picture was presented originally at the meeting of the American Academy of Ophthalmology and Otolaryngology in October, 1943. Through an oversight, the name of Dr. Jackson as co-author was omitted in the program of this meeting, and the names of Dr. Jackson and the writer, as co-authors, were omitted in the program of the American Laryngological, Rhinological and Otolological Society meeting in June, 1944, when the film was presented again.

3. After removal of the pars recta, stimulation of the pars obliqua causes a movement of the cricoid ring, mainly in the horizontal plane toward the stimulated side. There is only a slight upward movement visible. Simultaneous stimulation of both oblique portions effects a slight upward and backward pull of the cricoid ring.

4. After removal of the pars obliqua, stimulation of the pars recta causes an upward movement of the cricoid ring. No outward movement visible.

5. Upon stimulation of the cricothyroid muscles, the vocal cords elongate and the vocal processes approximate each other.

6. In some of our experiments we observed spontaneous movements of the cricoid ring, this structure moving upwards synchronously with expiration.

*The Spontaneous Movements of the Cricoid Ring:* This phenomenon has not been widely noted. It is not mentioned in any current textbook. Reviewing the literature, we were able to find only four authors reporting the occurrence of this phenomenon. These are: F. H. Hooper,<sup>16</sup> A. Kuttner and I. Katzenstein,<sup>17</sup> M. Grossmann<sup>18</sup> and P. I. Mink.<sup>19</sup>

It is remarkable that none of these authors referred to each other in their almost identical observations. Each apparently believed himself to be the first observer. Since we could find no report antedating the article of Hooper, we believe that he deserves the credit for its discovery. We suggest, therefore, that it be called "Hooper's phenomenon." His explanation reads as follows: "It is evident from these researches that the air escaping from the lungs produces a decided upward movement of the cricoid cartilage in addition to the general rise of the larynx, which movement increases in proportion to the force with which the air is expelled from the chest. The pressure of air causes a successive and independent upward movement of the cricoid onto the thyroid of which no mention has been made before." Hooper's explanation is based on experiments performed on excised larynges.

Mink observed the same phenomenon 33 years after Hooper and believed that the approximation of the cartilages during

expiration is due to the recoil after the release of the increased tracheal traction during inspiration.

Kuttner and Katzenstein, however, observed the occurrence of this phenomenon even after complete separation of the larynx from the trachea. We were able to substantiate these observations in our experiments. We think that the explanation presented by Hooper and Mink, as mechanical results caused by air pressure and tracheal traction, respectively, are not acceptable on the basis of our own observations. We believe the "Hooper's phenomenon" to be a centrally controlled expiratory action. It may be controlled immediately and directly by the respiratory center in the medulla. This view is supported by our observation of the fact that the phenomenon is reinforced when the air passage into the trachea is impaired by mucus, blood or mechanical occlusion of the distal end of the windpipe. This phenomenon may stand in a relationship to the  $\text{CO}_2$  tension of the blood and be comparable to the respiratory movements of the glottis.

There was, however, one interesting fact noted in our observations which should not be overlooked: several of our experimental animals did not present this phenomenon at all; furthermore, it disappeared when the animal was deeply anesthetized and when breathing was feeble, as in the period preceding death. The possibility of a cortical influence upon these spontaneous movements must be considered. It will be the task of future experiments to make this point clear.

These studies were performed only on dogs. The opportunity to duplicate them on human beings has not yet presented itself. I am not able to determine how far those observations are to be applied to man.

Lemere,<sup>20</sup> however, one of the most experienced experimenters on the larynx of the dog, makes the statement: "For all practical purposes the larynges of man and dog are identical."

#### SUMMARY.

1. A historical review concerning the studies of the anatomy and mechanism of the cricothyroid muscle was presented.

2. The recent view of Dr. Pressman in this connection was analyzed and objections to it were discussed.
3. Experimental results which sustain some of the objections were presented.
4. Additional information about the spontaneous movements of the cricoid ring were noted as auxiliary results of the investigations.

PROTOCOLS OF EXPERIMENTS.\*

Dog No. 3, May 28. Shepherd of 40 lbs.; 7.5 cc. nembutal injected, after 1½ hours 2 cc. more injected intravenously.

Sternohyoid muscle exposed. Stimulating draws the whole larynx and the trachea downwards.

Exposure of the cricothyroid muscles. There is to be observed a rhythmical spontaneous up and down movement of the cricoid ring synchronously with the respiration. Simultaneously with expiration the cricoid is pulled upward.

Unilateral stimulation of the cricothyroid muscle pulls the ring upward and laterally toward the stimulated side. Bilateral stimulation produces a jerking upward movement of the ring. Cutting of the sternohyoid muscle makes no changes.

Stimulation of the sternothyroid muscle pulls the larynx downward. The interspace between the cricoid and thyroid is unchanged. The same holds good for the respiratory movements of the cricoid ring.

(*Remark:* Dogs No. 1 and No. 2 behaved exactly like No. 3 except that the spontaneous movement of the cricoid ring was not observed.)

Dog No. 4, June 8. Weight 12 lbs. Intravenous injection of 6 cc. pentothal sodium. Animal ceased breathing after two minutes. It was kept alive by artificial respiration. Stimulation of the cricothyroid muscle unilaterally and bilaterally. Moving picture taken. Spontaneous movement of the cricoid ring was not present.

\*The aid of Dr. Samuel Elgart in performing several of these experiments is gratefully acknowledged.

Dog No. 5, June 15. Weight 24 lbs. Injection of 11 cc. nembutal after etherization of the animal. Immediately after injection, breathing and heart beat stops. Intracardial injection of adrenalin. Artificial respiration. Animal does not recover. Exposure of cricothyroid muscle. Resection of pars recta on the right side. Stimulation with electric current shows only movement of the ring to the right side. There is almost no upward movement. Resection of pars obliqua on the left. Stimulation. Slight upward movement, no outward movement.

Dog No. 6. Since the animal has already been used for pharmacological experiments, only a few experiments on the excised larynx were performed.

Dog No. 7, June 28. Weight 30 lbs. Injection of 13.5 cc. nembutal. Moving pictures taken of spontaneous respiratory movements of the vocal cords synchronously with the spontaneous movements of the cricoid ring. Moving picture taken of glottis on stimulation of the cricothyroid muscle.

Dog No. 8, July 16, 1943. Weight 22 lbs. Already experimented on by Dr. Jackson. Animal is tracheotomized. The trachea is completely separated at the level of the seventh ring. The spontaneous movements of the cricoid ring are distinctly visible but not as violent as in the previous cases. By closing the tracheostoma with the finger, respiration becomes more violent and likewise the movements of the cricoid ring.

Dog No. 9, July 29, 1943. Shepherd, 26 lbs. Pars recta on both sides removed. Pictures taken of cricoid ring on stimulation of pars obliqua. Larynx exposed and pictures taken on stimulation of abductors. Spontaneous movements in this animal were not distinct.

Dog No. 10, Aug. 2, 1943. Dark Schnauzer, 16 kg. Etherized and injected with nembutal gradually up to 5 cc. Cricothyroid muscle exposed. Respiratory movements of ring very distinct. These movements persist even after separation of larynx from trachea. Pictures taken. Tracing of abdominal respiration and simultaneous tracing of cricoid ring.

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Dog No. 11, September 28, 1943. Stimulation of pars recta showing the vertical pull of this portion of muscle approximating the cricoid ring to the lower border of thyroid cartilage.

Dog No. 12, Sept. 28, 1943. Weight 30 lbs. Showing spontaneous respiratory movements of the cricoid ring. Simultaneous stimulation of both oblique portions; slight upward and backward pull of cricoid ring. Trachea is completely cut off. Movement of ring persists.

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**TOTAL MONAURAL DEAFNESS FOR SPEECH, BUT  
NOT FOR THE SPEECH FREQUENCIES.  
MISLEADING THRESHOLD AUDIOGRAMS.\***

**EDMUND PRINCE FOWLER, M.D.,  
New York.**

"Word deafness" is a condition in which although there is recognition for other sounds there is a bilateral loss of hearing for speech.<sup>1</sup>

"Word deafness" may be developmental or acquired and in the latter case is indicative of damage to the temporal lobe, presumably of the dominant or both hemispheres. It is, in essence, a "cortical deafness." It occurs only with other language disabilities,<sup>2</sup> as distorted speech (paraplasia), jargon speech, etc. The hearing phenomenon I here report is quite distinct from this.

I have observed two patients† with a monaural total, or almost total acquired inability to recognize familiar words or language (lalognosis), although the speech frequencies, cadence and intensity variations of articulate speech were sensed. There was a loss of hearing for speech (articulation), without a sufficient loss for the frequencies used for hearing speech to account for it. There was no loss of ability to phonate, or any loss of memory for the sound or meaning of words heard by way of the opposite ear. Near voices appeared loud enough in the speech deafened ear, but sounded like the roar of a crowd; like a loud over-all frequency noise. The sounds heard were useless as an aid to hearing speech. A hearing aid was of no use to the affected ear. In the opposite ear the hearing was excellent.

\*Read at the Seventy-seventh Annual Meeting of the American Otological Society, Inc., New York, June 5, 1944.

†One of these patients was sent to me by Dr. Franz Altmann, and my observations were confirmed by him. The other had been examined by several otologists and neurologists but the phenomenon was not noticed.

I am indebted to Dr. Lyons, Dr. Lorente de Nò, Dr. Crowe, Dr. Guild and Dr. Orton for their interest and constructive criticism.

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In both instances there was a history of attacks of vertigo and either ipsilateral or bilateral tinnitus (Ménière's symptom complex), both of which gradually diminished with time and treatment. This suggests that the disorder probably

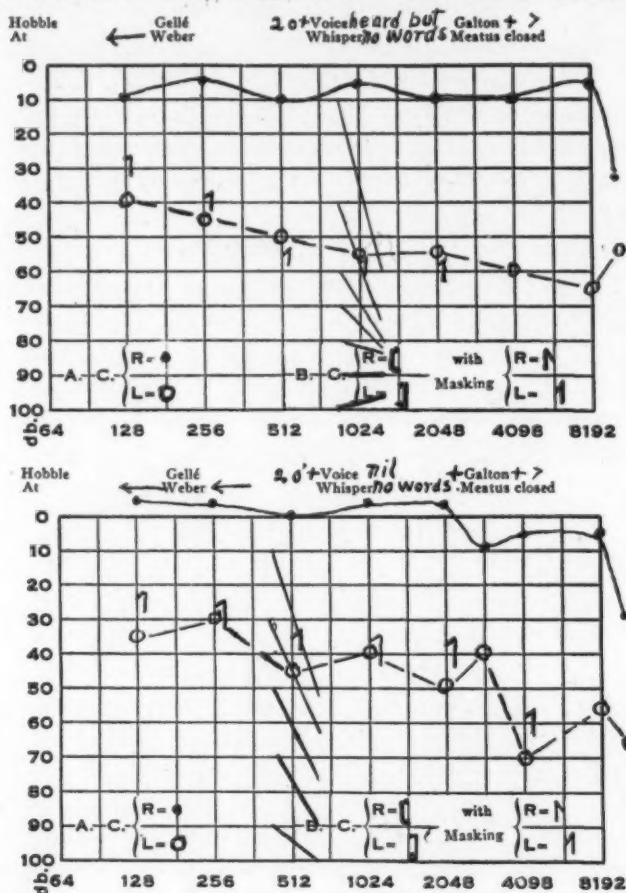


Fig. 1. Audiograms of two patients showing near normal hearing in the right ears and moderately severe losses in the left ears. Note that A.C. and B.C. are approximately the same, and the recruitment phenomenon is indicated for "A" at 1,024 and for "B" at 512. The recruitment phenomenon was present at all frequencies, which is positive proof that the lesion was in the neural mechanism. Neither of these patients could hear the spoken voice no matter how much it was amplified.

affected both divisions of the VIIIth nerve, but not necessarily only before it enters the brain. I was unable to correlate the condition with labyrinthine hydrops or herniation of the endolymph membranes. Moreover, in these latter conditions when some hearing has been retained, no one has reported an inability to hear and understand loud speech in the affected ear.

In the two cases here reported there was only a moderately severe loss of hearing in the affected ear, the most important speech frequencies being down only 45 to 50 db. below normal (see Fig. 1). Bone conduction and air conduction were noticeably impaired at most frequencies and the recruitment phenomenon was present at all frequencies. This observation definitely shows that the hearing loss was caused by a neural lesion and not by a neurosis or psychosis; it also proves that there was a quantitative discrimination as to loudness in the affected ear.

As in most monaural or unequal binaural severe nerve deafness, there was a difference in timbre between the two ears (a binaural displacusis). Loud pure tones sounded doubled like a quick echo. Bilaterally equal loudness of identical tones was sensed as higher in pitch in the deafened ear. This effect seemed greater than that which occurs in usual cases of nerve deafness with similar threshold losses. It increased with binaurally equal increases in loudness and was less noticeable for the high frequencies. This proves that there was a pitch discrimination in the affected ear.\*

In both patients there was an over-all frequency tinnitus in the deafened ear which was constant and difficult to mask.†<sup>5</sup> This tinnitus added to the confusion and masking effects caused by the noisy character of all the sounds heard in the speech deafened ear, but did not exclusively account for the very severe or total loss of hearing for speech.

\*A greater difference in frequency is required for minimal detectable discrimination in frequency for the high than for the low tones.

†In my opinion, tinnitus which is difficult to mask is associated with disorders central to the cochlea.

## DISCUSSION.

In right-handed people the dominant (kinesthetic) cortex is on the left side of the brain (vice versa in left-handed people), the right cortical speech center is dormant or subservient to the left center and is functionally inoperative if the left cortex functions properly. Presumably such was the case in these patients as both were right-handed and in both the neurological examination was negative except for the symptoms described (see Fig. 2).

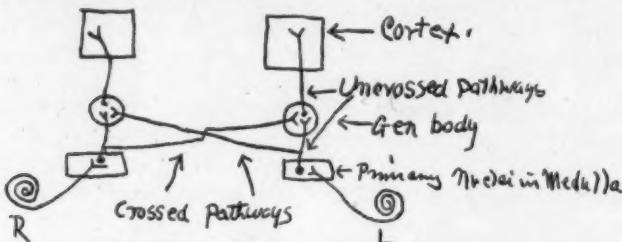


Fig. 2. A theoretical explanation of the "Fowler phenomenon."

Is the lesion to be sought for in the homolateral, the contralateral or the crossover mechanism? It seems illogical to think of its being located in the primary nuclei on the side of the good ear, because then it would presumably have to affect the hearing for sounds heard by the perfect hearing ear, and this did not occur.

As far as we know, each cochlea is represented in the cortex of both sides of the brain. This is demonstrated by the retention of hearing for all sounds after removal of either hemisphere in humans (Dandy, 1930-1932; Gardner, 1933). The same is true after affections or removal of the corpora quadrigemina, geniculate bodies or the lateral lemniscus on one side of the brain.

It has also been shown that "crossed fibres of the auditory system are approximately equal in acoustic value to the uncrossed components." (Mettler, *et. al.*, 1934) (Culler).

It is not known whether a subordinate cortex is capable of sensing speech received from the ear on the same side, when

the opposite dominant side of the brain is functioning satisfactorily. If it does not, this need not preclude the retention of fairly good hearing for sounds other than speech (for any or all of the frequencies), because sounds other than speech may have bilateral functional representation.

The central nuclei and auditory tracks are crowded, and the circulation to contiguous parts is so similar that it is difficult to conceive of severe lesions being long confined to the auditory neurones. Ultimately there would also be a tendency to affect the other neurones and the tracts to both sides of the brain (auditory and vestibular).

There is no question that the central pathway relay stations (central nuclei) help to analyze the different patterns of impulses, although a certain elemental analysis is previously made in the cochlea (Lorente de Nò, 1933). There is also no question that the threshold audiogram demonstrates a combination of all the lesions causing loss of hearing at any and all frequencies, in both the cochlea and the central auditory neurones; but, I believe, only in the cochlea in the absence of classical "mind deafness," "speech deafness" or "word deafness," or other central or cortical neurological signs.

If the phenomenon is, as in the two cases reported, always on the side ipsilateral to the dominant cortex, a shift in dominance to the opposite side of the brain would restore hearing for speech in the affected ear only if the lesion is above the main crossover level above the primary nuclei. It is not known whether such a shift can occur without a shift in all phases of dominance, but it also is not known that it cannot occur. I have a strong belief that it can and does occur under certain circumstances.

It is possible that the "monaural speech deafness" I have described might be due to some unknown pattern of degeneration in the cochlea, but in neither instance do the observed degrees and distributions of frequency loss alone appear sufficient to account for it. It is improbable that the lesion is entirely cortical, because when the opposite ear hears and understands speech, one cortex must be functioning well, and

presumably only one cortex is necessary for understanding speech heard by way of either ear.

Of course, many factors enter into all interpretative phenomena but these patients were alert and efficient individuals. There was no evidence of mental deficiency or any "psycho-acoust-asthenia."

The "monaural speech deafness" phenomenon must be differentiated from a deafness for speech wherein language is heard and understood with difficulty because of marked hearing losses, particularly in the upper half of the frequency scale. In all such instances, although there is a dislocation of the loudness and frequency patterns, it is still possible to make speech more intelligible by proper selective amplification and, to some extent, the brain in such instances seems able to accentuate or interpolate the faint or missing high tones; to conjure them from the dislocated speech patterns. This is possible because high frequency speech sounds are not discrete, being made up of broad bands of frequency, like blowing, buzzing, hissing or frying sounds, which do not need to be heard as clearly as the low frequencies to be recognized and used for hearing speech.\* Moreover, they can be sensed in part by the sound and rhythm of their low tone components.

What I have just said may be demonstrated by listening to speech at a great distance, because most of the high frequencies in speech are not heard at great distances and yet many words can be recognized. It is surprising how little hearing is needed, even in important frequency areas, to enable people to hear and interpret speech.

The brain seems able to shut off or ignore the poorer of two ears when it is hearing speech sounds so faint (or distorted) that they contribute little or nothing to the hearing of the opposite better hearing ear. This is a common psychological effect observed in bilaterally unequal hearing, and an allowance has been made for it in my method for estimating the percentage of capacity to hear speech.<sup>3</sup> Everyone con-

\*No two persons employ or enjoy the same intensity-frequency speech patterns.

centrates on hearing with his better ear, but if the latter is masked out, the worse ear even in very severe cochlea deafness is usually available for hearing loud speech.

The following experiment produces something like this bilaterally unequal hearing phenomenon. Listen to two radios, receiving the same broadcast, one with good radio reception opposite the right ear, and the other receiving a faint or otherwise distorted radio reception opposite the left ear. Under these circumstances in order to hear and understand the radio speech one must concentrate on the right ear, the ear hearing the better reception, and mentally exclude as far as possible the left ear, which hears the poorer reception.

I see no reason why "central speech deafness" cannot occur and be unilateral or bilateral, complicated by various patterns of nerve deafness and conduction deafness, and be congenital or acquired. It is not due to a degeneration from nonuse, because even very severe deafness does not cause it. It is possible that as in the optic nuclei, after loss of the eye, there may be a degeneration in the central auditory nuclei after total or partial loss of the end-organ.

Many children in schools for the deaf show a total loss of hearing for "speech" although their threshold audiograms may show losses at the most useful speech frequencies as little as 50 to 60 db. below normal. Some of these children suffer from classical "cortical word deafness," others from lack of education in the understanding of language, but some, I believe, may suffer from a bilateral "central speech deafness." Although these latter children cannot understand or mimic speech, even when using powerful hearing aids, they are not necessarily primarily mentally deficient. They should not be placed in schools for normal hearing children or with mentally deficient children; they belong in properly conducted schools for the deaf.

The phenomenon I have observed illustrates one of the many reasons why one cannot simply make an audiogram for a right and left ear and allocate a percentage loss of capacity to hear speech or a constant ratio of increment of percentage loss for the differences between the decibel losses

in the better and the worse ear. *It is evident that threshold audiograms alone do not necessarily reveal the true capacity for understanding speech and are not infallible criteria for diagnosis or for prescribing of hearing aids.*

The threshold and well over threshold audiometric graphs in these two cases are flat curves, which mean that most of the speech frequencies are equally affected. This is not the pattern of loss usually encountered in cochlear nerve deafness. In cochlear deafness there is regularly (but not always) a much greater loss for the high than the low frequencies by both A. C. and B. C. To my mind this also suggests an extra cochlear-neural mechanism involvement.

Several lesions associated with severe or total deafness for speech are known to involve the central nuclei or tracts. For instance, meningoencephalitis, causing dense glial scars involving the extra- and intrameningeal parts of the ventral cochlea nucleus and the acoustic tuberculum, may leave in its wake scattered and atrophied ganglion cells. After epidemic meningitis and as sequelae to measles, scarlatina, typhoid and influenza and many other bacterial and virus infections, there is occasionally a dramatic destruction in the central auditory apparatus with permanent deafness, although the cochlear nerve may be preserved.

In very old people there are always some circulatory disturbances and one often observes a progressive loss of hearing without proportionate losses in the speech frequencies. Lesions have been observed in the medulla and pons correlated with degenerative processes of aging.<sup>6</sup> I have suggested that mechanisms central to the cochlea, may at least in part be involved in old age deafness.<sup>7</sup>

Circulatory disturbances associated with deafness, tinnitus and vertigo also occur in the young and middle-aged. As I have pointed out,<sup>5</sup> they may be due to lesions central to the cochlea, which if repeated cause a localized anoxemia and spotty or mass degeneration in the medulla and pons. It would be strange if sometimes they did not involve at least the primary auditory and vestibular nuclei in the medulla.

The prognosis in the cases I have encountered appears excellent insofar as the good ear is concerned, because there has been no change in the hearing in this ear. The threat of involvement of this side of the head did not materialize. In one of the two cases, after four years, there was some return of hearing for the spoken word if the intensity of speech was not too low or too high. In the other patient, as far as I know, there is no change in either ear.) In one instance, not here reported because it was not so clear cut an example of the phenomena, I observed a subsequent total deafness for all sounds in the affected ear.

#### TREATMENT.

The only preventative measures I can suggest are watchfulness for the first signs of cranial nerve involvement; a complete otological and laboratory check-up and in all disease (virus, bacterial or toxic) associated with nerve deafness an earlier and better diagnosis. This holds true for all forms of nerve deafness.

The question arises: Is it possible, while one cortex remains dominant, to restore the speech deafened ear by re-educating a subordinate cortex (or dominant cortex) to understand the distorted speech? In view of the considerable recovery in one of these patients, it would seem a logical possibility, but I have thus far been unable to persuade myself or my patients seriously to undertake any planned re-education along these lines. Naturally no one cares to bother much with an ear which seems totally deaf for speech, when he can hear fairly or very well with his opposite ear.

It is apparent that the phenomenon I have described does not fit into the present concept of the pathologic physiology of the neural mechanism of hearing; however, it has many interesting implications, and may lead to something worth while. The physiologist and the otologist have concentrated so much upon the cochlea that the central neurones have been relatively neglected, and yet in these pathways there is an elaborate spacial representation and an extension and elaboration of the signs picked up in the cochlea. It is my contention that many audiograms commonly interpreted as repre-

senting wholly cochlear lesions also represent lesions of the central neurons. I have herein shown examples of, probably, two such instances. A careful study of serial sections of the auditory tracts, nuclei and centers in subjects who have shown the phenomena I have described, and who have been properly examined clinically and audiometrically, will, I believe, aid in solving this mystery.

#### SUMMARY.

The following hypotheses are suggested as probable explanations for the phenomenon of "total monaural deafness for speech without comparable loss of hearing for the speech frequencies":

1. A psychological exclusion of the deafened ear to speech.
2. Insufficient speech pattern transmission or reception.
3. A lesion in the crossover pathways (to a contralateral dominant cortex). A lesion in the uncrossed pathways (to a homolateral dominant cortex).
4. An anoxemia depending upon circulatory stasis from autonomic nervous mechanism episodes, in the homo- or contralateral tracts, which temporarily or permanently eliminates one or both of these tracts sufficiently to interfere with reception of proper neural patterns by the dominant cortex.\* (Too many pieces of the speech pattern are missing.)
5. A total or crippling lack of crossing of the auditory pathways.
6. A total or unusual crossing of the auditory pathways.

Dr. de No and Dr. Lyons will elaborate on these hypotheses in their discussions.

Analysis and correlation of the observations I have here set forth lead me to the conclusion that the syndrome described, *i.e.*, monaural deafness for speech without sufficient loss of hearing for the speech frequencies to account for it, and without a loss of ability to remember or to produce

\*It has been shown that there is a splitting or rupturing of axons in the neuroma at points of severe nerve trauma, whether toxic or mechanical, and that such lesions cause a dispersion or scattering of innervation to several localities by neurofibrils from a single axon.<sup>4</sup>

speech properly and usually with a persistent tinnitus difficult to mask (and maybe a transitory vertigo) may in part at least be due to lesions central to the end-organ; in its primary nuclei or somewhere in the central auditory neurones to the same or the opposite side of the brain (or

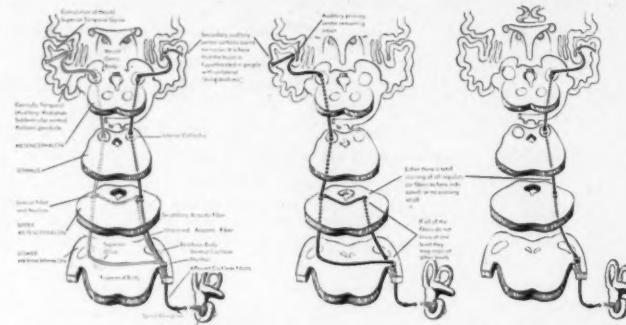


Fig. 3. Diagram of the Pathways for Speech (Simplified)

Since the cortex as well as the geniculocerebellar body receive fibres from the two sides, it is difficult to understand how a lesion in one of the hemispheres, or in one geniculocerebellar body, could prevent hearing speech with one ear but not with the other. A lesion in the geniculocerebellar body, or in the cortex on the dominant side should cause disturbances in the sensations mediated by either ear.

Since the L. cochlea allows the patients to hear the speech frequencies we are forced to conclude that unless the impulses transmitted by the L. cochlea nerve to the centers are insufficient for a correct analysis in the cortex, that there is a lesion in the centers that prevents correct analysis.

both), depending on whether the symptoms are in the early homolateral or contralateral to the dominant cortex. Fig. 3 is a simplified diagram of the pathways for speech, and reasons for my conclusions.

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140 East 54th Street.

## RECURRENT RETROTONSILLAR HEMORRHAGE.\*

JULIUS W. MCCALL, M.D., and WM. G. STOVER, M.D.,  
Cleveland.

The problem of massive hemorrhage in tonsillar and para-pharyngeal infection is, at best, one of grave urgency and doubtful prognosis. This case is presented not because of any new or unusual method of treatment but because of the unusual complications.

### CASE HISTORY.

F. M., a five-year-old white male, was first seen June 29, 1944, complaining of pain in the right ear and swelling in the region of the right mandible. Examination revealed normal ears and some injection and edema of the right tonsil. There was a cervical adenitis with 38.5° C. temperature.

July 7, 1944: There was a marked increase in the swelling of the right peritonsillar tissue. Simple incision was made, but no purulent material was seen. Temperature at this time was 38.5° C.

July 10, 1944: The tonsillar and peritonsillar swelling began to cause slight dyspnea and dysphagia associated with trismus. The incision was explored, followed immediately by a profuse hemorrhage, controlled by packing. The patient was sent to the hospital and given sulfadiazine. Laboratory findings: W. B. C., 16,000; hemoglobin, 3.19 M.

July 13, 1944: Patient was referred to Dr. Lawrence C. Meredith, Elyria, Ohio, and admitted to St. Luke's Hospital, Cleveland. Examination at this time revealed an acutely ill child. Temperature, 39.5° C. Pulse, 140; respiration, 28. Right cervical adenopathy associated with edema of the parotid area and neck. The right tonsil was touching the left side of the throat, with a clot-filled incision in right anterior pillar. There was also edema of the right side of the floor of the mouth. The incision was reopened, and a massive hemorrhage ensued, which was controlled with difficulty by pressure. Citrated blood and plasma were given. Then, because of marked respiratory difficulty, an emergency tracheotomy was performed under intravenous ether. The right external carotid was ligated. An attempt was made to drain the abscess externally, but no pocket was found. Re-examination of the peritonsillar incision again met with profuse hemorrhage. The common carotid artery was tied at this time, but this had no effect on the hemorrhage. Pressure on the left common carotid artery did not diminish the bleeding; hemorrhage was controlled only by packing and digital pressure. The edema now involved the entire right side of the scalp, eyelids, face, and neck to the midline. The patient was returned to his room.

Four hours later the ligature of the right common carotid was removed without difficulty. Treatment was chiefly supportive with daily small

\*From the Department of Otolaryngology, St. Luke's Hospital, Cleveland. Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Oct. 17, 1944.

transfusions of citrated blood until red cell count and hemoglobin estimation were normal. A total of 2,400 cc. citrated blood and plasma was given. Penicillin was given intramuscularly with a total dosage of 480,000 Oxford units.

July 14, 1944: The patient was unable to take fluids because of the peritonsillar swelling, so an intranasal feeding tube was introduced.

July 18, 1944: The patient's condition was remarkably improved, being afebrile and able to take liquids by mouth.

July 18 and 19, 1944: A biopsy was taken from the right tonsillar area. This showed acute inflammatory tissue on pathological examination. Cultures from this area were not conclusive.

July 22, 1944: The ninth day of admission, a massive spontaneous hemorrhage occurred from the former incised right retrotonsillar area. This was controlled by pressure, the patient was given 400 cc. of citrated blood on two occasions and he improved rapidly. The facial and cervical edema was subsiding, but some cervical adenitis was present. Throat practically normal except for slight swelling in the posterior pillar and lateral wall of the pharynx.

July 30, 1944: The patient was discharged, but on the way home had a profuse hemorrhage, so that he was admitted to another hospital, where the tonsillar bleeding was controlled by pressure. Transfusions of citrated blood were given, a total of 1,100 cc. Convalescence was uneventful, and on Aug. 5 the tracheotomy tube was removed.

Examination of Aug. 30 revealed a normal throat, a few palpable lymph nodes, tracheotomy and cervical incisions healed; however, for the first time there was noted a complete right hemiparesis of the tongue which had improved by Sept. 30.

#### COMMENT.

Any consideration of the source of massive hemorrhage from peritonsillar or parapharyngeal infection is purely conjectural unless the vessel is isolated.

This case is no exception; however, the large amounts of blood lost with each hemorrhage, in an associated cervical infection, lead us to suspect an arterial source. As ligation of the right common carotid artery, and pressure on the left common, did not control the bleeding, we are forced to conclude that the bleeding was not arterial. If the bleeding was venous, such a massive hemorrhage could come only from the internal jugular vein. Unfortunately, the patient's condition was so grave that further exploration of the neck could not be made.

The ligation of the common carotid artery caused no cerebral complications, probably due to the relative short time the common carotid was ligated; *i.e.*, four hours.

The hemorrhages on the ninth and sixteenth days after admission are not unusual, as no bleeding point was ligated, and the periodicity is such that weakening of any thrombus must be considered.

There is no doubt that the use of penicillin was of great importance in the cure of the infectious process.

Paresis of the facial and hypoglossal nerves are noted in jugular fossa infection. This also leads us to suspect the internal jugular vein as the source of hemorrhage. The return of function of the left hypoglossal nerve was noted Sept. 30.

#### SUMMARY.

Massive hemorrhage associated with peritonsillar or parapharyngeal infection is an alarming condition and one in which the source of the hemorrhage cannot be determined accurately in all cases. The massive edema of the face, the temporary paresis of the hypoglossal nerve; and that ligation of the right common carotid artery and pressure on the left did not control the bleeding forces us to conclude that the hemorrhage was venous in origin, and probably from the right internal jugular vein.

610 Rose Building.

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#### AMERICAN BOARD OF OTOLARYNGOLOGY.

The American Board of Otolaryngology will conduct examinations on the following dates:

June 5-6-7-8, 1945, Hotel Waldorf-Astoria, New York, N. Y.  
Oct. 3-4-5-6, 1945, Palmer House, Chicago, Ill.

For information write to Dr. Dean M. Lierle, Secretary-Treasurer, University Hospital, Iowa City, Iowa.

OTITIC MENINGITIS DUE TO BACILLUS PROTEUS,  
JUGULAR SINUS THROMBOSIS, SEPTICEMIA DUE  
TO STREPTOCOCCUS VIRIDANS, THORACIC  
AND CARDIAC COMPLICATIONS,  
RECOVERY.

E. LEE MYERS, M.D.,  
St. Louis.

Kortenhaus,<sup>1</sup> in 1930, reported only six cases of meningitis caused by the *B. proteus*. Dr. Josephine Neal,<sup>2</sup> in her review of 2,000 cases of meningitis, found two cases which were associated with other organisms. Gerzog,<sup>3</sup> in 1939, stated that only nine cases of *B. proteus* meningitis were reported, and only one recovered. Simon Stein<sup>4</sup> reported a tonsillectomy done for malignancy, complicated by mastoidectomy and meningitis due to *B. proteus*, and followed by recovery. McGovern<sup>5</sup> is of the opinion that *B. proteus* has an affinity for vascular structures, forms putrefactive necrosis with extreme toxemia, and can no longer be classified as a harmless saprophytic organism.

In reporting one case of *B. proteus* meningitis, we felt that the unusual type of jugular sinus thrombosis which defied ligation or resection justified the following case report:

CASE REPORT.

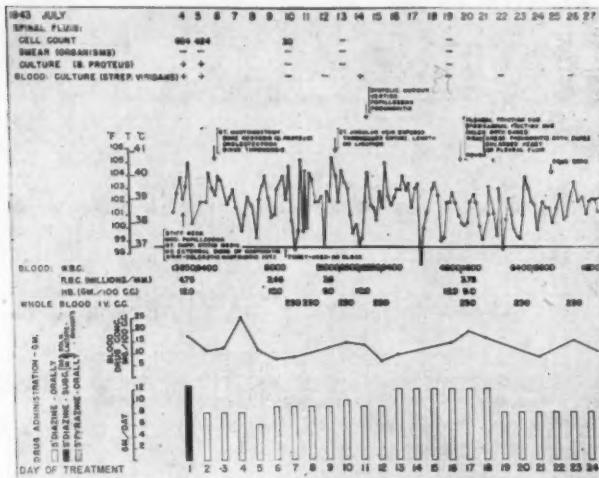
F. H., a nine-year-old boy, had a history of chronic intermittent suppurative otitis media of the right ear for eight years. He suffered with headaches, especially when the ear was dry, and complained of dizziness at times. At our first examination, July 3, 1943, the patient was in opisthotonus, and there was definite pain over the right mastoid. A smear from a spinal tap erroneously classified the case as epidemic meningitis. The following morning at the St. Louis Isolation Hospital, in consultation with Dr. Roland Klemme, a neurological surgeon, it was decided that the case was a definite otitic meningitis.

*Operation, Right Mastoid:* A fistula of the antrum was encountered from which much foul smelling pus welled up. An olive-sized cholesteatoma filled the mastoid cavity, and in an attempt to enucleate it, the knee of

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the sinus was damaged. This was packed with iodoform-vaseline gauze to control bleeding.

A spinal fluid culture revealed the presence of *B. proteus*, which we thought to be a contaminant, and a culture of material from the mastoid wound also showed a pure culture of *B. proteus*. Blood culture was positive for streptococcus viridans on several occasions, and the spinal fluid continued to be positive for *B. proteus*. From July 8 to July 13, the child's temperature spiked. Several unsuccessful attempts were made to get a blood culture from the internal jugular by direct thrust. Because of bilateral ankle clonus, the presence of streptococcus viridans in the blood stream, and the spiking temperature, it was decided that a search for a thrombus be made.

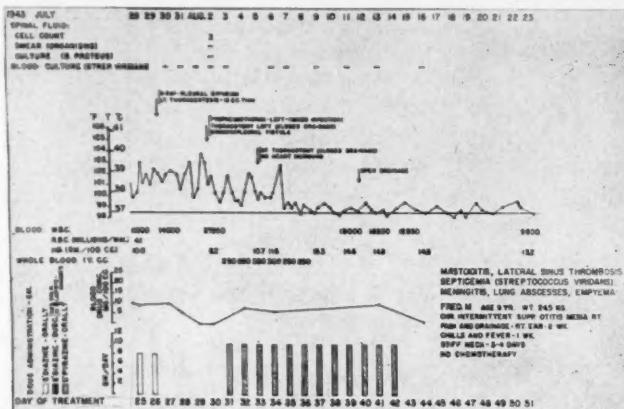


**Jugular Incision:** The right jugular vein was located with much difficulty and was found to be red and rubbery. Needling for a culture was impossible, and in trying to get below the rubbery section, the clavicle was reached. A ligation in the chest was then considered. Dr. Everts A. Graham thought that a ligation on the right side was impractical since the right innominate vein was entirely too short; however, he believed that had it been the left side, the ligation would have been feasible. Hence we were forced to rely on the sulfonamides, transfusions and supportive treatment. Schmelke's solution of azochloramide was used for the open mastoid wound.

Numerous chest complications with cardiac involvements made it necessary to transfer the child to the St. Louis Children's Hospital, where Dr. Alexis F. Hartmann and his staff gave the child most excellent care. Immediately after entry, the patient was seen by Dr. J. K. Poppe, of the chest surgery service, and was fluoroscoped. At that time pneumothorax and a fluid level were seen on the left with the heart shifted to the right.

On the right side there was a fluid level with a large collection of supernatant air above, but at that time it was impossible to tell if it were a pyopneumothorax or a subdiaphragmatic abscess with pneumoperitoneum. An intercostal thoracotomy was then performed on the left and the catheter attached for closed drainage under water. This relieved the patient markedly, and he began to breathe normally.

During this time, his right ear had continued to drain slightly and he was again placed on chemotherapy (sulfapyrazine by mouth 0.4 gm./kgm. body weight/24 hours), which was continued for 12 days. Daily blood cultures were continued but were without growth. He was given multiple transfusions of whole blood until his infection subsided. On Aug. 5, a diagnostic thoracentesis on the right proved that the fluid and air were



in the pleural space; therefore, a right intercostal thoracotomy was done and closed drainage instituted. Cultures of this pus grew out a multiplicity of organisms. Closed drainage was continued for seven days; other open drainage continued. From then on, convalescence was definitely established. By Sept. 7, the chest was completely healed, and by Oct. 5, under the care of the ear, nose and throat service, the mastoid operative site was healed. He gained weight rapidly, and no further heart involvement was noticed. By Nov. 1, he was completely well, having gained from his admission weight of 24 kgm. to 32 kgm.

I especially thank the personnel of the St. Louis Isolation Hospital and Dr. Freeman and Dr. Erganian for their untiring efforts towards the saving of this child's life. I also thank Dr. William G. Klingberg for summarizing all the important information in chart form.

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207-208 Wall Building.

**PHENYLPROPYLMETHYLAMINE.**  
**CLINICAL STUDY OF A NEW VOLATILE NASAL**  
**VASOCONSTRICTOR.**

HOWARD L. STITT, M.D.,  
Cincinnati.

This report is a study, over a period of 40 months, of a new nasal vasoconstrictor, phenylpropylmethylamine,\* used by inhalation in a series of 250 patients.

A nasal decongestant is probably the most useful single drug in the management of rhinological conditions. It is extremely important, therefore, that such a drug should not interfere with normal nasal physiology or function in producing undesirable local immediate or secondary tissue reactions. It would be ideal also if its use is not attended by any stimulating effect upon the cardiovascular or central nervous system.

The most desirable and widely useful nasal decongestant would be one that is effective both by inhalation and topical application. Phenylpropylmethylamine base is volatile and, therefore, is effective by inhalation; its salts are stable and in solution are active on topical application.

The only volatile vasopressor amines heretofore available for use by inhalation give adequate decongestion, but in some cases produce undesirable local immediate and secondary tissue reactions cause stimulation of the central nervous system and, occasionally, of the cardiovascular system.

For example, in our experience, inhalation of the previously available volatile amines produces blanching of the nasal mucosa and thus tends to disguise the real status of the nasal tissues. Their use is followed in some cases by a drying and scaling of the mucosa. Following the period of

\*Vonedrine brand. The Wm. S. Merrell Co., Cincinnati.

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decongestion, there often results a secondary turgescence or congestion. Quite often inhalation of their vapors causes a marked euphoria and stimulation of the central nervous system leading to nervousness and insomnia.

In attempting to overcome these undesirable features and obtain an effective decongestant, we started using routinely in office practice an inhaler prepared from the new vaso-pressor amine, phenylpropylmethylamine.

#### PHARMACOLOGY OF PHENYLPROPYLMETHYLAMINE.

Pharmacological studies<sup>1</sup> of phenylpropylmethylamine show that the toxicity of this compound is of the same order as ephedrine and about one-half that of amphetamine. The effect on the cardiovascular system and the bronchioles is very similar both quantitatively and qualitatively to that elicited by amphetamine; but it produces very little if any central stimulation in the experimental animal.

Its effect was studied on the living ciliated epithelium of the experimental animal, according to the method of Proetz.<sup>2</sup> There was no inhibition of ciliary activity.

Although it would seem from this pharmacological study that in humans phenylpropylmethylamine would have pressor action, Glaser<sup>3</sup> found that on oral administration to humans of 75 to 200 mg. daily over a period of five or six months, *no stimulating effect upon the cardiovascular or central nervous systems resulted*. It did not produce a pressor action, nor an increase in pulse rate. There was no euphoria, nervousness or insomnia observed at this dosage level.

#### CLINICAL USE OF PHENYLPROPYLMETHYLAMINE BY INHALATION.

For the past 40 months an inhaler containing phenylpropylmethylamine has been used adjunctively as a nasal decongestant in the management of 250 patients with rhinological conditions accompanied by nasal congestion. The conditions in which it was used principally were nasal allergy (hay fever, house dust sensitivity, etc.), nasal congestion accom-

panying acute or chronic rhinitis, sinusitis, mixed infection or pus infection of the nasopharynx accompanied by post-nasal discharge.

The inhaler was used routinely as a nasal decongestant: 1. prior to rhinological examination, 2. for reinstating the patency of the Eustachian tube, and 3. by both children and adults between office visits to maintain an adequate nasal airway.

Special attention was paid to rapidity, degree and duration of shrinking action, immediate and secondary effect on nasal tissues, and the presence or absence of undesirable systemic actions.

#### RESULTS AND COMMENT.

Over a period exceeding three years, we have been able to draw definite conclusions that this inhaler possesses certain desirable characteristics.

It could be used satisfactorily prior to rhinological examination by having the patient when seated in the chair take one long inhalation through the inhaler in each nostril. Within a minute or two, adequate shrinking had occurred which greatly facilitated direct examination of the nasal tissues. Most decongestants cannot be used in this manner because they blanch the mucosa by contracting the superficial blood vessels of the mucous epithelium, causing a local temporary deficiency of blood. This obscures the actual degree of the inflammatory mucosal reaction and disturbs nasal physiology.

It is most likely that blanching is an undesirable action in a nasal decongestant, for it would seem that mucosal hyperemia may serve the same useful purposes in the nasal tissue in the presence of inflammation that it does in other tissues of the body. It is the deeper erectile sinuses in the nasal tissue covering the turbinates that need to be constricted to provide patency of the airway.

The phenylpropylmethylamine inhaler wick, placed in a special apparatus for introducing air or vapors into the

Eustachian tube, provides a means of restoring the patency of the tube in the presence of congestive obstruction without producing local irritation or central stimulation.

It was observed that following inhalation of the phenylpropylmethylamine vapor, shrinking of the tissues occurred rapidly and the ostia of the sinuses were opened, facilitating drainage; the secretions were rendered less viscid; in some cases where congestion was of such degree that liquid medication could not be introduced by any method, inhalation of the vapor gave sufficient shrinkage to facilitate topical applications.

Particularly interesting was the effect of the use of the phenylpropylmethylamine inhaler on the nasal tissues. The degree of shrinking action was satisfactory, being equally as great as that of other volatile amines. The period of decongestion was somewhat longer and there was no compensatory congestion or turgescence following the period of decongestion.

When the inhaler was used repeatedly over long periods of time, there were no untoward local tissue reactions such as dryness or scaling, nor was there burning on inhalation.

In the treatment of patients with postnasal discharge caused by excessive refined carbohydrate intake, use of the inhaler, combined with reduction of carbohydrate intake, proved efficacious in reducing discharge and rendering the patient more comfortable. There were no symptoms, in either children or adults, of central stimulation, such as euphoria, insomnia, nervousness or pressor action. This feature permitted use of the inhaler as often as necessary to maintain patency of the nasal airway.

#### SUMMARY.

1. A new volatile amine, phenylpropylmethylamine, has been used by inhalation for decongesting the nasal tissues in a series of 250 rhinological patients with nasal congestion resulting from various causes. This report covers a period of study of 40 months.

2. Phenylpropylmethylamine has certain advantages in the clinical practice of otolaryngology as follows:

- a. decongestion without blanching
- b. no evidence of irritation
- c. satisfactory degree of shrinkage and duration of action
- d. no undesirable immediate or secondary local tissue reactions, such as drying, scaling or secondary rebound congestion
- e. no central nervous system or cardiovascular stimulation
- f. safe for use in children as well as adults.

3. The importance of these characteristics in rhinological practice is discussed.

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19 Garfield Place.

## VITAMINS AND THE EYE, EAR, NOSE AND THROAT.\*

By DR. ISAAC H. JONES, DR. HAROLD S. MUCKLESTON,  
DR. EUGENE R. LEWIS and DR. GILBERT ROY OWEN,  
Los Angeles, Calif.

It seems to the observer that there has been a remarkable sequence of events concerning this problem of nutrition as it relates to the eye, ear, nose and throat. Intense research in many parts of the world was set into motion by the discovery of vitamins. The student of the literature found it difficult to keep abreast with the discovery of each new vitamin — and next with the synthesis of many of them. Then clinicians so promptly applied the new facts that each one in our specialties soon realized the necessity of being alert to detect evidence of vitamin deficiency in the tissues and functions of the eye, ear, nose and throat. This has been done so well and so quickly that during the past two or three years little new information has been added to the clinical experience which was so soon available after the original scientific research.

It is now clear however that many of the problems are more complex than they appeared at first — and the patient should come to realize this no less than the doctor. Despite the paucity of "new vitamins and new cures" considerable knowledge of the essentials is already available. The patient in his innocence asks "Are vitamins good?" We should have a ready answer to his earnest question. Between doctor and patient a very close relationship exists; and we can contribute to this if we make it a point to show him the difference between the "vitamin racket" and the true value of vitamins. The cheap advertising which is so repellent to us — especially over the radio — is too often accepted at its face value by the general public. For the laity the message is vividly por-

\*From talks before the Mid-Winter Convention of the Research Study Club, Los Angeles.

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trayed in a cartoon by Lichty — the druggist is exhibiting a bottle — "Madam, you ask: 'Is this a good tonic?' Why, this product started out as a mere local broadcast but it is now on the national hook-up with an 87-piece orchestra." Even the most gullible patient cannot fail to grasp the idea that the problems of nutrition are not so simple as that.

In sharp contrast, it would be difficult to overstate the true value of nutrition studies — in fact they may turn out to be the most valuable contribution of the Twentieth Century. To present properly what might well be called the "romance of the vitamins" one might use the phrases of an official report of the Royal Air Force concerning the war effort — "One should have something of the qualities of Herodotus, Socrates and Voltaire. If one were tireless in collecting facts, expert in checking them and concise in presenting them — then the story could be properly told."

Important as the known facts are today, the sequence falls into that old pattern with which we are all familiar: A discovery — hailed with a more or less wild enthusiasm that here at last was "the answer" to our problem; then gradually knowledge of its limitations; and finally a sane estimate of the importance of the new discovery. For example, the story of the vitamins is like that of the sulphonamides. We now know their great value — but we also know their limitations as well as their dangers. Before the American College of Physicians in conclave assembled, an avalanche of first reports set forth the magic results of sulphanilamide. A grand old Nestor of our profession then rose and quietly said: "That's right, boys — get in your reports early." In their search for gold, prospectors always are wary of pyrites — "Fool's Gold" — glittering but valueless. Pyridoxin was hailed as the long-sought remedy for Parkinson's disease, pantothenic acid as the restorer of lost hair pigment — both turned out to be therapeutic pyrites.

The clinician has had his disappointments — failing to bring back lost function. Finding no other cause for optic neuritis, nerve deafness or anosmia and discovering inadequacy of diet, he has used appropriate vitamins — without

effect. Once in a while however he succeeds. A patient complained of paresthesias of the extremities, "pains around the heart," vertigo, staggering and a distressing loss of memory. Cardiologic examination was negative and a thorough study by an internist completely failed to reveal any abnormality. The patient was told "If you keep on talking about your symptoms your best friends will begin to avoid you." Because of the vertigo he was sent to us. We noted some blood on his tongue, and on inquiry learned of the presence of blood in his mouth every morning for nine months. It was further found that he had not taken citrus fruits for years; he disliked them intensely. After administration of "C," orally and by needle, citrus fruits, tomato juice and baked potatoes, the bleeding soon ceased and the other symptoms gradually disappeared. It was surprising to find in Southern California this frank case of scurvy. In another patient we noted skin lesions suggestive of pellagra. The history showed such a loss of strength and energy as to compel him to stop work. He had had a week of clinical study as a result of which he had been advised to have an operation for anal fissure. On large doses of B Complex reinforced with niacinamide, the skin condition improved promptly. Within two months his general strength had returned, he was back at his work and the anal fissure was healed. This therapeutic test confirmed the diagnosis of pellagra. Such experiences make us wonder how many similar deficiencies we are overlooking in our daily practice.

Any gross deficiency gives obvious signs and symptoms—as in frank beri-beri, scurvy and pellagra. To detect a moderate or mild deficiency the clinician can depend only on more or less indefinite signs and symptoms plus laboratory findings—if any. Our suggestion has been that the problem be approached by observing *tissue*. The tissues of the body which are most easily observed are those of the skin, eye, ear, nose and throat. Some years ago we advanced a working concept which we termed "the embryologic approach." The three germ layers all demand vitamins; consequently, in service to our patients it is of immediate importance to learn all we possibly can of the observed defects of vitamin deficiency.

on the derivatives of the three germ layers. This concept might be expressed as follows:

1. Each tissue has need of many vitamins.
2. Altho each vitamin affects various tissues, it appears that a special relationship exists between vitamin and germ layer.
3. It seems that each germ layer demands an oil-soluble and a water-soluble vitamin. The Ectoderm requires "A" (oil-soluble) and the B Complex (water-soluble). The Mesoderm requires "C" (water-soluble), and "D" (oil-soluble); the Entoderm requires "A" (oil-soluble) and the B Complex (water-soluble).
4. The Ectoderm and Entoderm seem to have a common need in that they demand the same vitamins — "A" and the B Complex.
5. The Mesoderm requires "C" for the development of connective tissue and "D" for the development of bony tissues.

If this concept is correct — that each germ layer has a particular relationship to certain vitamins and not to others — we then have a rational approach to therapy. If we as clinicians note a lesion of the eye, ear, nose or throat, then, knowing of what germ layer this particular tissue is a derivative, we have an immediate clue as to what vitamin or group of vitamins is needed.

If the individual were to receive perfect food, perfectly prepared — all would be well. McCollum<sup>1</sup> makes clear that Samson, David and the original Marathon runner demonstrated that it is not necessary to take vitamins in pills; similarly Venus de Milo, Aspasia and Cleopatra derived their charm, as the others derived their strength, from natural foods only. Consequently a study of tissue requires far more than a knowledge of vitamins. It is the raw material that constitutes the tissue — the proteins, carbohydrates, fats, minerals and mostly, water. The structure and nature of each tissue is determined by the varying proportions of these raw materials. Tissues are burned up in the process of

living — and this wear and tear necessitates replacements. Although we cannot have a full understanding of the miracle of metabolism, we already know certain essentials. After ingestion, digestion and distribution of the pabulum, it is still raw material — in fact it is still raw material while being selected by the cell. Only when particles of raw material have finally been appropriated and incorporated by the cell, do they become living tissue. It is here that the activators play their part. Raw materials and their products in the body are valueless without the activators — just as the activators are valueless without the raw materials. As we see it today the whole problem might be summarized: There are two classes of activators — the intrinsic and the extrinsic. Those from within the body are the endocrines and those from without are the vitamins.

The concept of deficiency disease is an old one. As Greene<sup>2</sup> states, it began with a discovery by Kramer in 1720 that scurvy could be cured by the citrus juices — though the discoverer believed that the citrus juice was producing a positive action, like a drug. The next real step came more than a century and a half later when Takaki discovered that beri-beri was in some way related to incorrect diet. At about the same time it became generally recognized that rickets also was a dietetic disease. By 1912 sufficient knowledge of scurvy, beri-beri and rickets had accumulated for the Polish scientist Funk to invent the word "vitamin" and to propound the modern theory of deficiency disease.

As to the significance of nutrition Rowntree<sup>3</sup> makes a succinct statement: Life rests on chemical activity; this is sustained by nutrition; man lives to work, eats to live — and works to eat and live. Life, health and efficiency turn on nutrition; and yet, although scientifically much is known about nutrition, all over the world this knowledge is used but little. Of all the millions who have been examined for service in our armed forces, more than one-third have been found unacceptable. An analysis of examinations made during peace time showed that 3.2 per cent had defects specifically and almost solely due to nutritional deficiency — such as beri-beri, scurvy, pellagra, malnutrition, rickets and night-

blindness. This rate of 3.2 per cent, however, is an underestimate. It concerns only part of the picture. We know that nutritional deficiency is encountered in a large number of diseases. During peace time when physical standards were high, 188,000 of the first million men rejected were disqualified for dental defects alone—the leading cause for rejection. A large proportion of these was due to dental caries and it is becoming more and more recognized that nutrition is the main cause of dental caries. We also know that many moderate and mild deficiencies result in lesions of the eye, mouth, gums, lungs, cardio-vascular system, kidneys and skin—not to mention mental, musculo-skeletal and endocrine defects. If such conditions are included, and well they may be, in estimates of nutritional deficiencies, then the figure becomes multiplied many times. The gross defects in the frank marked deficiencies total 3.2 per cent; but if we include the moderate and mild deficiencies, we reach a total of 43 per cent.

In 1929 J. B. S. Haldane wrote: "We have, it is true, a department humorously called 'the Ministry of Health' but it is not realized that State action influences the national health except through such agencies as drains, water supply and medical officers of health." Contrast that with a recent report: "The distribution of food was planned with the assistance of nutrition experts so as to assure each section of the commonwealth an equitable share of the food needs for the maintenance of health." Elvehjem<sup>4</sup> regards the United Nations' Conference on Food and Agriculture at Hot Springs, Va., as potentially one of the most important international conferences ever held; it recommended that governments should immediately undertake to increase their food resources and improve the diets of their people. The greatest obstacle to overcome will continue to be lack of fundamental information. Elvehjem stresses the importance of considering little-known factors which may prove vital. On a synthetic diet containing "A," "B<sub>1</sub>," "B<sub>2</sub>," "D," "E," niacin, pyridoxine, pantothenic acid and choline—rats grow almost normally; deficiencies were corrected by adding "K," biotin and folic acid. Hamsters grow and survive only when

biotin and inisitol are added. Mice require added inisitol; chicks require added biotin and preparations from liver or yeast carrying two factors distinct from folic acid. Cotton rats require added liver preparations in addition to biotin, inisitol and para-amino-benzoic acid. The monkey shows poor growth, leukopenia and dysentery; but crude folic acid supplies all necessary factors. Guinea pigs grow normally only when a number of natural products are added. Some of these unisolated factors may prove unimportant but it appears probable that others may prove essential.

A group from New York — McDevitt, Dove, Dove and Wright,<sup>5</sup> went to a secluded region in Newfoundland and made a careful study of its isolated people. For a large part of every year, they are on a diet lacking important food factors. They grow potatoes, cabbages and turnips; during certain periods they have many types of sea-food; but they have very few cows or goats — and therefore very limited milk supply. These primitive people, who have used milk only to flavor their tea, actually have a traditional distaste for milk. Limited supplies of citrus fruits are available during the summer months and for intermittent periods during the winter. These are considered as tasty adjuncts but rarely as a necessary component of the diet. The foodstuffs available to the men in the lumber camps during the winter months and to the fishermen who go down to Labrador are even more restricted than those available to the general population. The diet is high in carbohydrates and fats, moderately high in proteins, but very poor in milk, fruits, butter, eggs, greens and vegetables, except during brief seasons. Laboratory studies of several hundred individuals showed that the blood "C" levels could be correlated with the available "C" in the foodstuffs for the several months. As the supply of fresh foods decreased, the blood levels of "C" were reduced. The lowest level was in April. Those who showed a saturation in "C" during October were in the deficiency group in the early spring. In seven instances samples of blood from the umbilical cord were obtained at the time of delivery. The "C" levels in the blood plasma from the umbilical cord were higher than in the maternal blood, in each instance — even

when the maternal level was extremely low. Their studies demonstrated that whereas there is a selective filtration of "C" by the placenta, there is a possibility of latent scurvy at birth if the mother has been on a diet deficient in "C." A very important finding in this study was the evidence of a lack of the B Complex. A very large number of these people showed the following signs and symptoms — constipation (of 3 to 8 days or more between stools), absence or diminution of reflexes, foot-drop, numbness and tingling of the extremities and areas of disturbed sensation; swelling, soreness and discoloration of the tongue, and cheilosis and nasolabial scaliness.

It is downright startling to read Goodhart's<sup>6</sup> summary of conditions observed in manufacturing plants in which cafeteria meals are served to employees. Much of his material is obtained from a publication of the National Research Council. The loss in vitamin values in the preparation of the foods is serious — from 36.3 per cent to 91.9 per cent of "B<sub>1</sub>" and from 29.5 per cent to 82 per cent of "C." Only "B<sub>2</sub>" proved quite stable to the method of preparation used. In many of the factories milk is offered, but is used by only a minority of the employees, in some places by 2 per cent, in others by 10 to 25 per cent — in rare instances by 40 per cent. It appears that the nutritional status of large numbers of our industrial workers is below a level compatible with optimal health and physical and mental efficiency.

The general subject of nutrition and the human eye is discussed by Wilder,<sup>7</sup> who considers that some of those engaged in these studies have been over-enthusiastic whereas others, with self-satisfied skepticism, have closed their eyes to advances of importance. The principal benefactors of the knowledge of nutrition will be the children. The damage done by bad food habits by the time that adult life is reached is probably extensive — with premature senile changes as a consequence. However, even in the aged some degree of reversibility may be attained by the long-time use of certain nutrients. To attribute tissue lesions simply to old age is shirking a professional responsibility. Senescence is a product of tissue damage—not a cause. When the culture medium

is regularly renewed in vitro, tissue cultures do not become senescent. These cultures in an optimal controlled environment are immortal. Few persons at all times throughout life have received diets that are adequate in all particulars. There is a tendency to discount much of what the laboratory rat has taught us; in point of fact — the rat in eating habits and digestive mechanism is closer kin to man than is the dog. Abnormalities develop in the eye in the course of most diseases associated with so-called degeneration. The severe acute disturbances of nutrition are reflected by specific lesions in the eye and it is not unreasonable to expect that further study will reveal reflections there of various types of chronic malnutrition. In this research the ophthalmologist should be able to contribute most importantly. The beams from his ophthalmoscope and slit-lamp ought to light the path of human progress from poor to better health.

Much work has been done to show the effect of vitamins on the cornea. The dramatic effect of cod-liver oil in healing keratomalacia led Williamson-Noble\* to the supposition that it might be equally successful in other corneal lesions. The B Complex is of importance in the metabolism of the cornea — the most important factor being "B<sub>2</sub>." As to the lens, the absence of cataract in deficiency diseases such as scurvy, pellagra and beri-beri would seem to show that the human lens is not so sensitive as the cornea — to avitaminosis. However, experimental work shows that vitamins play a considerable part in the metabolism of the lens. Cataract appears in rats as the result of a diet deficient in "B<sub>2</sub>." "C" is important in the metabolism of the lens; it is present in the aqueous in a concentration over ten times that in the blood plasma, and its absence in aphakia and in some forms of cataract seems to indicate that "C" is furnished by the lens. In the retina there are three vitamins — "C," "K" and "P" — deficiency of any of which will produce hemorrhages. In a "C" deficiency the characteristic lesion is the occurrence of capillary hemorrhages. "K" is believed to combine with an unknown product of the liver to form prothrombin. "P" probably has its action on the cells of the capillaries and increases their resistance to pressure. It is present in lemon and orange

juice. A sign of "P" deficiency is the occurrence of spontaneous petechial hemorrhages in parts of the body exposed to pressure. Such hemorrhages clear up when "P" is given.

Experimental withdrawal of "A" from the diet of sows prior to breeding brought on characteristic wobbling or weaving gaits, drooping of the ears, and loss of weight. Hale<sup>9</sup> reports that fifteen such animals were bred and produced litters of 4 to 14 pigs. Eye abnormalities in various combinations were observed in 6 litters; all pigs in these litters were actually blind. The defects ranged from bilateral absence of eyes to dissimilarity in the size of the globes. In the remaining 9 litters none of the pigs were born blind. A striking parallel occurred in the experience of each of two Texas farmers, whose live-stock suffered owing to drought conditions from lack of green feed, and therefore from lack of "A." One farmer found that in a litter of fourteen all the pigs were born blind; the other farmer made the same discovery in a litter of seven pigs. In the latter case the dam was later bred to one of her blind offspring, after both had received rations containing "A." She then gave birth to normal pigs. Hale believes that no hereditary factor can be held responsible for the blindness of these pigs and lays the blame at the door of an "A" deficiency.

By spectroscopic analysis Wald<sup>10</sup> identifies two closely similar chromogens which he names "A<sub>1</sub>" and "A<sub>2</sub>." He pursues the development of visual function along the ascent from invertebrates to vertebrates, taking marine and fresh water fishes for his chief study. In arthropods and molluscs are found components of the rhodopsin — "A<sub>1</sub>" system; only vertebrates possess porphyropsin and "A<sub>2</sub>." In general, fishes may be divided into two groups: Anadromous forms (swimming up-stream) — for example salmons which spawn in fresh water; and catadromous forms (swimming downstream) — for example fresh water eels which spawn in the sea. The former have primarily the porphyropsin system and "A<sub>2</sub>"; the latter have predominantly rhodopsin and "A<sub>1</sub>." All known visual systems are based chemically upon the two "A" vitamins. "A" undergoes reversible changes. During light adaptation "A" is liberated from the retina when its

capacity to hold "A" is exceeded; this is diffused into contiguous tissues and into the circulation; contrariwise during dark adaptation the retina recaptures "A," binding it with rhodopsin. When the general systemic level of "A" becomes lower, the level of the retinal cycle falls, including also the concentration of rhodopsin — upon which the sensitivity of the rods depends. The resulting rise in visual threshold is night-blindness. The dependence of visual function in animals upon carotene and "A" has a close parallel in plants; the presence in them of carotenoid complexes is the basis of phototropism — the function by which they turn in the direction of a source of light.

The strictly academic lines followed by the biologist Wald are matched by those chosen by Yudkin, Robertson and Yudkin<sup>11</sup> in their extensive search for the visual threshold in apparently normal subjects. They examined 400 persons to determine the process of dark adaptation and the effect of "A" upon it. From this number 40 laboratory technicians were tested repeatedly, 14 of these intensively, while taking either "A" (24,000 I.U. daily) or carotene (20,000 I.U. daily) in the form of carrots for several weeks. Carefully checked observations demonstrated that "A" produced consistent increase in sensitivity to light in the periphery of the retina. In some cases "A" produced also an increase in macular sensitivity to light. Such increases frequently occurred without speeding up the time required for dark adaptation. Many cases proved to be only transient — 7 days later the ability to adapt had deteriorated toward the original level. A modified Crookes' dark adaptation apparatus was used.

The cure of color vision defects by "A" reported by Dunlap and Loken<sup>12,13</sup> caused Elder<sup>14</sup> to conduct experiments. It seemed to Elder that what is well known of visual receptor function plus the demonstrable hereditary determinant and a tendency for color thresholds to remain constant under varied environmental conditions, suggested that the defect probably would not respond to vitamin therapy. In preliminary tests on 16 college students "A" was given, 25,000 mg. daily, for 8 weeks or more. Fourteen showed no improvement; two who had slight defects showed improvement. In

order to check the possibility that some benefit could be derived by a few individuals, extensive observations were then made under more rigid tests. Fifty-eight R.O.T.C. freshmen cadets showed various degrees of defective color vision. Fifty thousand mg. "A" were given every other day for 8 weeks, the subjects being required to swallow the capsules at a dispensing station. After each had taken 1,400,000 mg. "A," all were retested under the same conditions. No significant improvement was found in any individual. Most of the records of response to the 62 plates of the American Optical and Ishihara tests were practically identical before and after taking the "A." The maximal improvement shown by any individual was a correction of three previous errors.

As the middle rays of the spectrum are the least irritating, especially the softer greens, a special lamp which offered this combination was used by Newton and Schade<sup>15</sup> to see if it would conserve the "A" in the visual purple. It did. Their tests showed that this type of illumination lessens eye-strain and conserves "A" in the retina.

A boy aged three served practically as a test animal, furnishing ample evidence of the danger in an over-administration of "A." Josephs<sup>16</sup> had this case under his observation in the hospital. From the age of 2 or 3 months, owing to the mother's enthusiasm for vitamin therapy, the child had received daily a teaspoonful of halibut liver oil, the equivalent of about 240,000 U.S.P. units of "A," and in addition an unknown amount of which he had drunk direct from the bottle. He showed loss of appetite and disinclination to play; tonsilectomy was followed by a severe hemorrhage for which he received three transfusions; his hair fell out, and the new growth was sparse, dry and coarse; his liver and spleen were enlarged, and his blood picture was that of hypoplastic anemia with leukopenia. Once the excessive amount of "A" in the serum had been found, the story of the almost incredible intake of "A" was drawn from the mother. After the withdrawal of extra "A" from his diet, the child's condition promptly began to improve; within six months his blood picture became normal, and the serum content of "A" was within normal limits. In the next two years and a half he

made very good progress, but his liver and spleen remained large, and his fingers were still clubbed. Josephs reviews the literature of the past twenty-five years, and to this case report added summaries of six others. Freakish dietaries and an over-indulgence in "A"-containing fruits and vegetables were to blame. Carotenemia commonly reveals itself in xanthosis cutis, or yellowness of the skin. Other manifestations may be found — loss of weight, low basal metabolic rate, hypotension and muscular weakness. The low metabolic rate may lead to a false diagnosis of hypothyroidism. These conditions improve rapidly on a sane adjustment of eating habits and a diet high in calories.

That a lack of the B Complex is the greatest single cause of precancerous mouth lesions is the conclusion of Martin and Koop,<sup>17</sup> after a study of 1500 cases of mouth cancer. Previous to this study they had not found any reference to this subject in the literature. It has been considered that such degenerative changes were initiated by some local irritant such as tobacco. Some authors stress the importance of tobacco, others syphilis, others sepsis. The classic belief, dating from Hippocrates, is in the importance of the trauma produced by sharp teeth. Degenerative mucous membrane changes are found in the majority of cases of mouth cancer. Most patients with cancer are already suffering from a mild to a marked avitaminosis B on admission. This lack tends to be aggravated by the necessarily restricted diet during the painful stages of mouth cancer. Supplementary vitamin therapy is one of the most important factors in the successful treatment of intra-oral cancer. There is also considerable evidence that the mucous membrane lesions of avitaminosis B are not confined to the oral cavity alone but affect the whole gastrointestinal tract. It is therefore possible that such degenerative changes are significant in the etiology of gastric and intestinal cancer as well as mouth cancer. It is reasonable to believe that one of the most effective means of prophylaxis against mouth cancer would be to increase the general intake of foods rich in the B Complex.

After two years of study, Holmes<sup>18</sup> advocates the use of "B<sub>1</sub>," 15 mg. daily, for at least two days before sailing or fly-

ing, as a defensive measure against seasickness or airsickness. He reports the experience of 24 men, habitually nauseated by rough seas, who took "B<sub>1</sub>" as prescribed, with complete relief. In six other men who had been drunk this treatment was unsuccessful.

Najjar and Holt<sup>19</sup> studied 9 males, 16 to 23 years of age, leading sedentary lives in an institution. They received 40 calories per kg. in a vitamin-free food mixture, unchanged during 18 months of observation. To this mixture were added the following vitamins, daily: "C" 25 mg., "B<sub>2</sub>" 1 mg., niacinamide 25 mg., calcium pantothenate 1 mg., pyridoxin 1 mg., choline chloride 5 mg., inositol 1 mg., paramidobenzoic acid 1 mg. and "B<sub>1</sub>" in varying quantities. During 18 months these subjects maintained weight and vigor. "B<sub>1</sub>" intake was then very gradually reduced from the initial dose of 1 mg. in order to ascertain the minimal "B<sub>1</sub>" intake which would prevent a "B<sub>1</sub>" deficiency. In the course of time the "B<sub>1</sub>" was gradually reduced to 0.1-0.2 mg. per day; this daily intake was continued for months — with no evidence of deficiency. Then "B<sub>1</sub>" was entirely omitted for 5 weeks — during which 4 subjects developed neuritis or edema, anorexia and occasional vomiting. Four subjects showed no signs of deficiency during 7 weeks without "B<sub>1</sub>." Stools of most subjects continued to show combined "B<sub>1</sub>" — yielding free "B<sub>1</sub>" on treatment with clarase. Further investigations indicated that intestinal bacteria actually produce "B<sub>1</sub>"; that such "B<sub>1</sub>" is absorbed by the colon; and that bacteriostatic effects of sulphonamide inhibit this biosynthesis of "B<sub>1</sub>" in the colon.

His experience with 97 patients in two years suggested to Castellanos<sup>20</sup> that a lack of "B<sub>2</sub>" is the cause of vernal conjunctivitis. He gave "B<sub>2</sub>" to all; 35 showed improvement on the 3rd or 4th day, and 62, in 10 to 15 days.

Ferguson<sup>21</sup> studied corneal vascularization in 76 cases out of 250 patients complaining of ocular fatigue. Seventeen were classified as "probably ariboflavinosis"; 7 of these did not remain long enough for conclusive observation. No note was made of seasonal incidence. In 13 cases on "B<sub>2</sub>" treatment for an adequate period the abnormal vascularization disappeared.

The degree of corneal vascularization was determined by Lyle, Macrae and Gardiner<sup>22</sup> in 4000 R.A.F. personnel at 10 stations in England and 12 overseas. They studied the effects of giving vitamins and highly nutritious foods. Vascularization was noted in many receiving excellent food; however they found more vascularization when the food was poor and less when the food was good. They suggest that other factors present in fruits and vegetables influence this condition more than does "B<sub>2</sub>." Moreover Fish<sup>23</sup> notes that ocular rosacea and ariboflavinosis show entirely different patterns. She also notes that rosacea is seasonal whereas ariboflavinosis is not. She agrees with those who consider that rosacea is not due to a lack of "B<sub>2</sub>."

In reporting a patient with restoration of vision, Shapiro<sup>24</sup> states a problem in clear terms. The metabolism of carbohydrate requires "B<sub>1</sub>," "B<sub>2</sub>" and niacin. These three vitamins are part of the enzyme systems involved. The active form of "B<sub>1</sub>" is cocarboxylase. Glucose is broken down into pyruvic acid; the "B<sub>1</sub>" enzymes are necessary to oxidize this pyruvic acid. It is the accumulation of pyruvic acid in the cell that results in the symptoms we find in B-Complex deficiencies. Abnormally high levels of pyruvic acid in the blood are found in patients with beri-beri or acute alcoholic neuritides, largely due to the lack of "B<sub>1</sub>." Persons of alcoholic habit are especially susceptible to the neurologic manifestations of a "B<sub>1</sub>" deficiency. Histologic examination of nerves in cases of neuritis reveals damage more severe in alcoholic than in non-alcoholic patients. The B-Complex requirement is proportional to the caloric intake — approximately 50 to 70 mg. per 100 calories. A moderately active man of 154 pounds requires daily at least 1.8 mg. "B<sub>1</sub>," 2.7 mg. "B<sub>2</sub>," and 18 mg. niacin. Neuritis of any type should spur the examiner to investigate relentlessly the alcoholic history and dietary habits. For 8 years a patient had worn satisfactory glasses for reading. When attempting to cross the street he stepped down off the sidewalk uncertainly. Everything went "blurry." He was troubled with pain in the soles of the feet when standing for prolonged periods. He also noted irregular periods of tinnitus — in both ears. He stated that he was a moderate

drinker of alcoholic beverages—but in the course of his study it was found that he had been drinking much more than at first admitted and that he had frequently gone without food. His vision was 5/200 bilateral, uncorrectible. The pupils were equal and regular and reacted to light and accommodation. There was a coarse tremor of the extended fingers. Romberg negative. The plantar reflex was absent in each foot; marked sweating of the feet. The patient exhibited an anxiety state, was inclined to be forgetful—his memory was somewhat defective even for recent events. B-Complex therapy was begun—but with very little effect until months had passed. After five months of treatment, however, most of the symptoms were gone. The right plantar reflex had returned; the left was still absent. He still had sweating of the feet and was subject to twinges of pain in the feet, especially with weather changes. His memory had improved and he had regained much of his ambition. Apprehension was minimal. Three months from the beginning of the B-Complex therapy his vision was normal—20/20 and Jaeger I in each eye. Apparently the main factor in his recovery was "B<sub>1</sub>" in large concentrated doses, given intramuscularly.

A determination by Philpot and Pirie<sup>25</sup> of the "B<sub>2</sub>" content of various eye tissues showed the highest amount in the cornea and in the meibomian and lacrymal glands. This suggests that the cornea obtains its "B<sub>2</sub>" from the eye secretion and not from the blood supply.

"B<sub>1</sub>," nicotinic acid and "B<sub>2</sub>" were tested by Novak and Adams<sup>26</sup> for their stability in whiskey (86.8 proof). Of the three only "B<sub>2</sub>" was found to decompose rapidly, 90 per cent being lost in 3 weeks. No measurable loss of "B<sub>1</sub>" and nicotinic acid occurred in six months.

A photographic study of the changes which occur in the cornea of rats that had been deprived of "B<sub>2</sub>" was made by Tisdall and McCreary.<sup>27</sup> When the animal was ready for study, it was anaesthetized, the thorax was opened and India ink was injected into the left heart. The anesthesia was deepened and the beats of the heart which occurred before death disseminated the India ink throughout the blood ves-

sels of the body including any new vessels which had formed in the cornea. The animal was immediately hung in a head-down position and as soon as possible photographs were taken of the eye. Under ordinary conditions the optimal requirements of "B<sub>2</sub>" are 2.5 to 3 mg. daily; however this substance is rapidly destroyed by light. It seemed reasonable that an individual exposed to a great deal of light would show an increased destruction of "B<sub>2</sub>" in the eye; this would necessitate a greater intake to maintain vision. With this in mind the authors made a study of aviators and their crews to determine if there were a lack of "B<sub>2</sub>" and a prevalence of corneal vascularization in these individuals exposed to so much light. It was found that apparently healthy individuals exposed to considerable glare in their daily routine did show evidences of vascularization of the cornea and had symptoms which have been attributed to the lack of "B<sub>2</sub>." Administration of large amounts of "B<sub>2</sub>" for a period of two months to one group of these men caused a progressive decrease in the vascularity in 70 per cent; and a clearing or improvement in symptoms in 95 per cent. Administration to another group of the same dosage for a period of only one month resulted in much less improvement in the vascularity but a marked improvement in symptoms. A third group received capsules, similar in appearance but containing no "B<sub>2</sub>"; there was no change in vascularity. Among the aviators in areas where milk, the best source of "B<sub>2</sub>," was not available, the prevalence and severity of corneal vascularization was markedly increased. The writers conclude that vascularity of the cornea among apparently healthy young adults in Canada is surprisingly high; it seems to vary with the amount of "B<sub>2</sub>" contained in the diet; also that "B<sub>2</sub>" in large dosage for a period of two months decreased the vascularization of the cornea in a large percentage of cases, and also caused a marked improvement in symptoms of eye fatigue in men exposed to glare in their flying duties.

Help in cases of Vincent's infection is found by Johnson<sup>28</sup> in the use of niacin. He finds that relatively small amounts are effective, for adults 25 to 50 mg. three times a day; for children 10 mg. or more according to age.

The effect of a lack of "C" on the metabolic rate of ethyl alcohol was studied by Jervis.<sup>29</sup> Guinea pigs were deprived of "C" until they showed loss of weight, joint tenderness and hemorrhages of paws. Animals in both deficient and control groups received only water for 18 hours preceding the experiment. They were kept fasting and at constant temperature during the experiment. A fixed dose of absolute alcohol (2 mg. per gm. body weight) was given intraperitoneally. This dose was diluted with 3 parts normal saline. Alcohol determinations were then made at hourly intervals. In all experiments the metabolic rate of alcohol was lower in the "C" deficient animals than in the normal controls. Factors which are known to alter the metabolism of alcohol were excluded. It is concluded that the metabolic rate of ethyl alcohol is significantly decreased when the organism is depleted of "C." This research might suggest that "Bacardi" or "Daiquiri" cocktails are better than the gin or whiskey mixtures which contain no lime or lemon juice.

In a series of 51 cases, Pelner<sup>30</sup> gave sulfadiazine, 1 gm. every four hours, and along with it 100 mg. of "C." None of his patients showed unfavorable reaction to the sulfadiazine, and all were free of any depression. Pelner makes no claim that "C" enhances the therapeutic value of the sulfonamide, but is convinced that it makes such treatment possible in cases where the drug alone would necessarily be reduced in amount or abandoned entirely.

Manwaring<sup>31</sup> gives a clear picture of our present knowledge of biotin. Steinitz in 1898 first showed that raw egg-white is poorly digested. Bateman later found that raw egg-white is thrown off in the stools of the dog, rat, rabbit and man; also that it exerts a toxic effect shown by diarrhoea and loss of weight. Twenty years later Boas found that rats develop a peculiar dermatitis and gradual loss of weight which eventually proved fatal, if they received an adequate well-balanced ration — except for a large excess of raw egg. György found that egg albumin is capable of inactivating biotin in vitro, due to the formation of a relatively indigestible compound — "avidin." This avidin produced toxic effects, presumably due to its power of binding or inactivating biotin,

thus preventing absorption of this necessary vitamin. In order to determine whether a similar "biotin blockade" occurs in man, Sydenstricker placed a small group of human volunteers on a diet containing an excess of raw egg-white. In three weeks all subjects showed skin desquamation which disappeared spontaneously. During the 7th and 8th weeks all subjects showed a grayish pallor of skin and mucous membranes with a return of the desquamation by the 9th week. Mild depression progressing to extreme lassitude, somnolence and a mild panic state were noted in most subjects, accompanied by muscular pains, hyperesthesia and localized paresthesia. There was a definite diminution in hemoglobin, a striking rise in serum cholesterol and an average biotin excretion of only 5 mg. daily as compared with previous excretion of 40 mg. At this time the subjects received daily biotin injections of 150 mg.; within three to five days the depression, muscular pains, precordial distress and anorexia were abolished; the ashy pallor disappeared, serum cholesterol was reduced to normal and daily urinary excretion of biotin rose to 55 mg. Sydenstricker concludes that such symptoms may appear if one-third of the daily caloric intake is supplied by egg-white. It has long been a practice of poultry-raisers to add charcoal to feeds under the impression that charcoal adsorbs bacterial toxins; Almquist and Zander, however, have shown that adding 2 per cent of charcoal to a diet containing adequate amount of all vitamins results in stunted growth, "curled-toe paralysis," incoordinations, subcutaneous hemorrhages, prolonged clotting-time and an eroded lining of the gizzard. They consider that charcoal absorbs numerous vitamins from the gastro-intestinal contents. Thus far the inactivation of vitamins has been of little clinical interest except in case of the prolonged use of mineral oil. The demonstration that excessive diet of raw egg may be equally deleterious is of suggestive clinical interest. However it is well to emphasize that cooking destroys the avidin, or "anti-biotin," in raw egg, and that its apparent toxicity is readily prevented by such biotin-rich foods as cabbage, spinach, liver, kidney and milk. Egg-yolk is rich in biotin but, unfortunately, contains only half the amount of this

essential vitamin needed to neutralize the "avidin" or "anti-biotin" in the accompanying egg-albumin.

Some individuals are much more susceptible to malaria than others. Although this has been an accepted fact no reason for it has yet been demonstrated. A careful study by Trager<sup>32</sup> found that chickens and ducks developed much more severe infections with the *Plasmodium lophurae*, if they were made deficient in biotin. A very mild degree of biotin deficiency sufficed to increase the susceptibility. Biotin is evidently a substance which affects the degree of natural susceptibility to malaria.

A symposium, presented by four Louisville physicians, gives a comprehensive review of "C" deficiency at various ages. Hollis,<sup>33</sup> recognizing the decline in the incidence of scurvy in infants, due to current practice of giving fruit juices, believes that "C" deficiency may explain cases of sudden death; he finds parallel in the experiences of ship's officers of sailing-ship days who observed sailors suffering from scurvy die suddenly and unexpectedly. Right-sided cardiac atrophy has been reported in such cases in both children and adults. He attributes benefit for a minority of asthmatics to the generous use of "C." In cases where allergic reactions forbid the taking of "C"-containing fruits juices, Limper<sup>34</sup> finds that children can assimilate the vitamin in its crystalline form, given by mouth or by injection. The same mode of administration is recommended if sore gums or stomatitis be an obstacle to the taking of tart fruit juices. The pathology of scurvy is reviewed by Dalo<sup>35</sup> who describes its effects upon gums, eyelids and conjunctivae. The oculist's encounter with "C" deficiency is handled by Leggett:<sup>36</sup> Normally "C" is found in lens and aqueous in relatively high amounts; the lens, in particular, has "C" in 12 to 20 times the proportion found in blood serum. There is a possible relation between "C" deficiency on the one hand and senile cataract and progressive myopia on the other.

What is the result of overdosage of "A" and "D"? With the collaboration of Agnes Fay Morgan, Becks<sup>37</sup> worked out an answer to this question from his study of dental and osse-

ous tissues in dogs. They chose two litters of cocker spaniels, and fed them on controlled dietaries for an average period of 308 days. Optimal doses of "A" and "D" are set at 800 U.S.P. units per kilogram and 72 U.S.P. units respectively. Excessive doses of the two vitamins are 10,000 U.S.P. units in each case. "A" given in either amount worked favorably in the production of sound bones and teeth. Becks found the same result from the use of "D" in optimal dosage, but from excessive use of "D" there resulted osteosclerosis of the jaw bone and paradental bone structures, malformation and malocclusion of the teeth, and the formation of many pulp stones. Becks believes that fish liver oils are a better source of "D" than irradiated ergosterol.

The tragedy of congenital syphilis involves the corneas of from one-third to one-half of its victims at some period of their lives. A considerable experience with the effectiveness of "E" (wheat germ oil) on the rate of absorption of tissue exudates in various conditions led Stone<sup>28</sup> to apply it in interstitial keratitis. Ten patients, from 7 to 42 years of age, with corneal lesions of from 3 months' to 35 years' duration, offered a wide range of severity and of previous antileutic and fever treatments. All showed marked visual impairment in one or both eyes; and all showed photophobia, vascular congestion and corneal opacities, both superficial and deep. "E" was given in capsules containing 50 mg. of mixed tocopherols from wheat germ oil concentrates, one capsule once or twice daily, usually in combination with the B Complex. Of the 10 patients, 2 also received artificial fever treatments after beginning their course of vitamin therapy. All 10 patients showed improvement within a week; by the end of the second or third week vascularization had disappeared in most of the patients as had the superficial exudates and opacities; deep opacities were much more slowly absorbed — one case requiring 18 months. The visual acuity showed marked improvement in several; in one the change was from light perception in one eye and counting fingers at two feet in the other eye to 20/20 in each eye. The gradual and continuous absorption of opacities of long-standing in patients receiving "E" therapy, irrespective of the amount of antileutic therapy,

suggests that other factors than the spirochete may be responsible for the corneal changes.

Studies with "K" were made by Abbott and Holden<sup>39</sup> on 120 patients with various diseases. The largest group comprised 36 cases of intestinal disorders. In several a low prothrombin level was raised to normal by "K." In a case of tumor obstructing the bile ducts, bleeding from the gums, bladder and gastrointestinal tract was stopped by the use of "K." Nasal hemorrhages occurred in a patient with cirrhosis of the liver; this failed to respond to "K." In general, patients with severe liver damage did not react to "K" therapy.

Studies by Davidson and MacDonald<sup>40</sup> indicate that the untoward effects of too large a dose of dicoumarol may be counteracted by the injection of "K<sub>1</sub> oxide." A transfusion of fresh blood also has the same effect. The synthetic "K" appears to work too slowly; it does not neutralize dicoumarol so quickly.

\* \* \* \* \*

How much more information may now be available we unfortunately are unable to know at the time of this writing, due to war conditions. Because of inadequate man-power two great medical libraries in this region are months behind in their bibliographic research.

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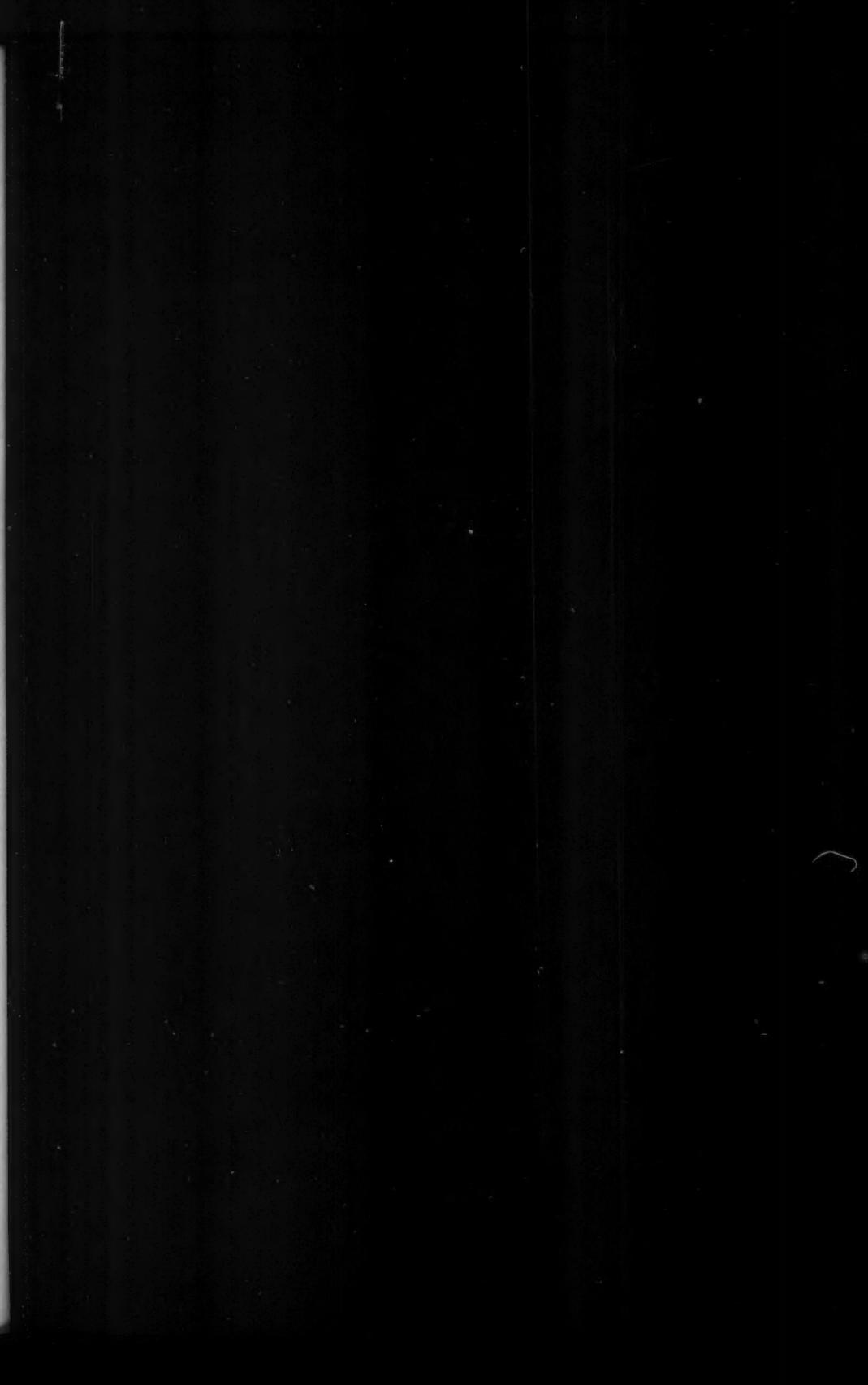
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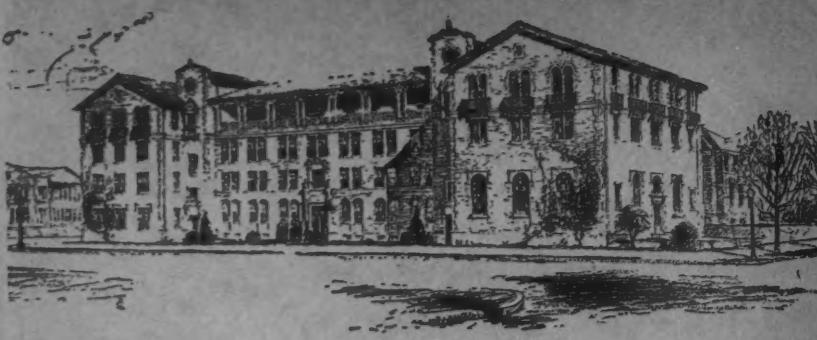
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